CHAPTER II

HISTORICAL

Distribution

1. Alkaloids and their occurrence.

The term alkaloid, meaning "alkali-like", was first proposed by the pharmacist, W. Meissner, in 1819 (Pelletier, 1919) for the fact that most of them are basic in nature and form salts with acids (Robinson, 1968). Being a heterogenous group of compounds, they are extremely difficult to be defined. Generally, all alkaloids are naturally occurring compounds having a rather complex structure with nitrogen atom in a heterocyclic ring and are physiologically active (Pelletier, 1969; Clause, Tyler and Brady, 1970). Almost all of the alkaloids occur in plants and practically all have been reproduced in the laboratory by chemical synthesis, but some of them are found in animals (Clause, Tyler and Brady, 1970). The best examples of animal alkaloids are bufotenine from the toad and in human urine (Swan, 1967), dehydrobufotenine from the toad, and samandarine from the salamander (Taylor, 1966).

Approximately two thousand alkaloids have been isolated and the structures of most of them are known. It has been stated that about 15-20 per cent of all vascular plants contain alkaloids (Swan, 1967).

They are rarely found in cryptogamia with the exception of ergot alkaloids, in gymnosperms, or monocotyledons. They occur abundantly in certain dicotyledons and particularly in Apocynaceae, Papaveraceae, Papilionaceae, Ranunculaceae, Rubiaceae, Rutaceae and Solanaceae (Pelletier, 1969).

The families which contain alkaloid bearing plants are listed below (Manske, 1950; Schultes, 1976).

A. Dicotyledons

Anonaceae
Apocynaceae
Aristolochiaceae
Asclepiadaceae
Anonaceae
Aristolochiaceae
Berberidaceae
Boraginaceae
Buxaceae
Cactaceae
Calycanthaceae
Caricaceae
Chenopodiaceae
Compositae
Convolvulaceae
Erythroxylaceae
Lauraceae
Lobeliaceae
Loganiaceae
Magnoliaceae
Menispermaceae
Monimiaceae
Papaveraceae
Papilionaceae
Piperaceae
Punicaceae
Ranunculaceae
Rhamnaceae
Rubiaceae
Rutaceae
Solanaceae
Umbelliferae

B. Monocotyledons

Amaryllidaceae
Dioscoreaceae
Gramineae
Liliaceae
Orchidaceae
Palmae
Roxburghiaceae (Stemonaceae)

C. Gymnospermae

Taxaceae
Gnetaceae

D. Pteridophytae

Equisetaceae
Lycopodiaceae

Indole alkaloids are the alkaloids containing an indole nucleus. A rough estimate is that more than one quarter of all known alkaloids are indoles (Robinson, 1968). All indole alkaloids occur in plants but, as mentioned earlier, some are found in animals, i.e. bufotenine (Swan, 1967) and dehydrobufotenine (Tayler, 1966).

While the distribution of indole alkaloids is broad, certain plant groups are noted for containing them. Among the seed plants the family Apocynaceae has been a very rich source of indoles. In this family the genera *Rauvolfia*,*Catharanthus* and *Aspidosperma* have been particularly well investigated. Another important source is the fungal genus *Claviceps*, which is known to contain more than two dozen different indole alkaloids (Robinson, 1968).

The complex indole alkaloids occur most frequently in the family Apocynaceae, Asclepiadaceae, Loganiaceae and Rubiaceae (Schultes, 1976). The more complicated indole alkaloids and the corresponding oxindole alkaloids having similar structures are distributed in the following genera :-

Alstonia (Saxton, 1965 b)
Catharanthus (Morton, 1977)
Corynenthe (Karrer and Salomon, 1926)
Mitragyna (Bentley, 1965)
Nauclea (Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974)
Picralima (Robinson and Thomas, 1954)
Pseudocinchona (Cu, Goutarel and Janot, 1957)
Rauvolfia (Müller, 1957)
Strychnos (Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974)
Uncaria (Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974).

2. Alkaloids isolated from species of *Uncaria*.

The alkaloids have been reported in species of *Uncaria* as follow:

Uncaria acida (Hunt.) Roxb. from Brunei, Indonesia and Malaysia.

Leaf : harmane, isorhynchophylline, rhynchophylline and its N-oxide (Phillipson, Hemingway and Ridsdale, 1978).

U. acida (Hunt.) Roxb. var. *papuana* Val. from New Guinea.

Leaf : 3-isoajmalicine, isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide, corynoxeine.

Leaf / stem : isorhynchophylline, rhynchophylline (Phillipson, Hemingway and Ridsdale, 1978).

U. africana G. Don from Zaire.

Leaf : ajmalicine, 3-isoajmalicine, 19-epi-ajmalicine, tetrahydroalstonine, dihydrocorynantheine, isomitraphylline, mitraphylline and its N-oxide, isorhynchophylline, rhynchophylline.

Leaf / stem : africanine (unknown structure) (Phillipson, Hemingway and Ridsdale, 1978).

U. africana G. Don var. *domatifera* Petit from Zaire.

Leaf : ajmalicine, 3-isoajmalicine, 19-epi-3-isoajmalicine, isomitraphylline, mitraphylline (Phillipson, Hemingway and Ridsdale, 1978).

U. africana G. Don var. *xerophila* Petit from Zaire.

Leaf : isomitraphylline, mitraphylline (Phillipson, Hemingway and Ridsdale, 1978).

U. angolensis Welw. from Guinéa.

Leaf : isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide (Phillipson, Hemingway and Ridsdale, 1978).

U. appendiculata Benth. from Indonesia, New Guinea, Solomon Islands.

Leaf : isomitraphylline and its N-oxide, mitraphylline, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide.

stem : isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide (Phillipson, Hemingway and Ridsdale, 1978).

U. attenuata Korth. from East Malaysia, Sumatra and West Java, Indonesia.

Leaf : 3-isoajmalicine, tetrahydroalstonine, rauniticine, 14-hydroxy-3-isorauniticine, akuammigine, dihydrocorynantheine, hirsutine, hirsuteine, epiallo-corynantheine, harmane, pseudoyohimbine, yohimbine, dihydrocorynantheine pseudoindoxyl, isomitraphylline and its N-oxide, mitraphylline and its N-oxide, speciophylline, uncarine A, uncarine B, isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide, isocorynoxeine, corynoxeine, rotundifoline, isorotundifoline, yohimbine oxindole (Phillipson and Hemingway, 1975 b; Phillipson, Hemingway and Ridsdale, 1978; Supavita, 1979).

Stem bark / stem wood : dihydrocorynantheine, hirsutine, hirsuteine, pseudoyohimbine, yohimbine isomer, isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide, isocorynoxeine, corynoxeine, yohimbine oxindole (Phillipson and Hemingway, 1975 b; Phillipson, Hemingway and Ridsdale, 1978).

U. avenia Val. from Indonesia, New Guinea.

Leaf : dihydrocorynantheine, isorhynchophylline, rhynchophylline

Stem : isorhynchophylline
(Phillipson, Hemingway and Ridsdale, 1978).

U. barbata Merr. from Borneo, Indonesia.

Leaf : harmane
(Phillipson, Hemingway and Ridsdale, 1978).

U. bernaysii F. v. Muell. from New Guinea.

Leaf : tetrahydroalstonine, akuammigine, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide
(Johns and Lamberton, 1966; Beecham, Hart, Johns and Lamberton, 1968; Phillipson and Hemingway, 1973 a; Phillipson, Hemingway and Ridsdale, 1978).

Stem : same as in the leaves
(Phillipson and Hemingway, 1973 a; Phillipson, Hemingway and Ridsdale, 1978).

Hook : isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide
(Phillipson and Hemingway, 1973 a).

Flower : ajmalicine, 3-isoajmalicine, tetrahydroalstonine, akuammigine, angustine, isomitraphylline, mitraphylline, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide (Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974; Phillipson, Hemingway and Ridsdale, 1978).

U. bernaysii F. v. Muell. forma *inermis* K. Schum. from New Guinea.

Leaf : isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide
(Phillipson, Hemingway and Ridsdale, 1978).

U. bernaysioides Merr. et Perry from New Guinea.

Leaf : isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide
(Phillipson, Hemingway and Ridsdale, 1978).

U. borneensis Havil. from Sumatra, Indonesia.

Leaf : harmane
(Phillipson, Hemingway and Ridsdale, 1978).

U. brevicarpa Elm. from Philippines.

Leaf : isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide
Fruit / seed : speciophylline
(Phillipson, Hemingway and Ridsdale, 1978).

U. bulusanensis Elm. from Philippines.

Leaf : 19-epi-3-isoajmalicine, dihydrocorynantheine, epiallo-corynantheine, rhynchophylline, rotundifoline, isorotundifoline, speciofoline,

corynoxine B
(Phillipson and Hemingway, 1975 b; Phillipson, Hemingway and Ridsdale, 1978).

U. callophylla Korth. from Indonesia, Malaysia, Singapore.

Leaf : dihydrocorynantheine, gambirine, isomitraphylline, mitraphylline, isorhynchophylline, rhynchophylline, harmane
(Phillipson and Hemingway, 1973 d; Phillipson, Hemingway and Ridsdale, 1978).

U. canescens Korth. from Indonesia, Malaysia, Thailand.

Leaf : harmane.
Stem : same as in the leaves
(Phillipson, Hemingway and Ridsdale, 1978).

U. cordata (Lour.) Merr. from New Guinea, West Java, Indonesia.

Leaf : isorhynchophylline, rhynchophylline.
Stem : same as in the leaves.
Flower : same as in the leaves
(Phillipson, Hemingway and Ridsdale, 1978).

U. dasyoneura Korth. from Indonesia, Malaysia, Thailand.

Leaf : roxburghine D, roxburghine E
(Phillipson, Hemingway and Ridsdale, 1978).

U. donisii Petit from Gabon.

Leaf : isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide
(Phillipson, Hemingway and Ridsdale, 1978).

U. elliptica R. Br. ex G. Don.

Leaf : roxburghines
(Phillipson and Hemingway, 1973 d; Phillipson, Hemingway and Ridsdale, 1978).

U. ferrea (Bl.) DC. from Malaysia, Philippines, Sarawak, Sumatra.

Leaf : harmane, isomitraphylline, mitraphylline and its N-oxide, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide
(Johns and Lamberton, 1966; Beecham, Hart, Johns and Lamberton, 1968; Phillipson, Hemingway and Ridsdale, 1978).

Flower : isomitraphylline, mitraphylline and its N-oxide, isopteropodine, pteropodine, speciophylline and its N-oxide, uncarine F.

Stem : harmane, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F
(Phillipson, Hemingway and Ridsdale, 1978).

U. ferruginea (Bl.) DC. from West Java, Indonesia.

Leaf : dihydrocorynantheine.

Flower : same as in the leaves.

Stem : same as in the leaves
(Phillipson, Hemingway and Ridsdale, 1978).

U. florida Vidal.

Leaf : isopteropodine, pteropodine, speciophylline (Aimi, Yamanaka, Endo, Sakai and Haginiwa, 1972; Phillipson, Hemingway and Ridsdale, 1978).

U. formosana (Matsum.) Hayata from Taiwan.

Leaf : isomitraphylline and its N-oxide, mitraphylline and its N-oxide, uncarine A, uncarine B.

Flower : 3-isoajmalicine, isomitraphylline, mitraphylline, uncarine A, uncarine B (Phillipson, Hemingway and Ridsdale, 1978).

U. gambir (Hunt.) Roxb. from Sumatra, Indonesia, Singapore.

gambir : gambirine, gambirtannine, oxogambirtannine, dihydrogambirtannine, neo-oxygambirtannine, ourouparine (Merlini, Mondelli, Nasini and Hesse, 1967 a; Saxton, 1968; Phillipson and Hemingway, 1973 d; Irie, Fukudome, Ohmori and Tanaka, 1975; Phillipson, Hemingway and Ridsdale, 1978).

Leaf : tetrahydroalstonine, dihydrocorynantheine, gambirine, isorhynchophylline, rhynchophylline, rotundifoline, roxburghine A, roxburghine B, roxburghine C, roxburghine D, roxburghine E (Merlini, Mondelli, Nasini and Hesse, 1967 a; Merlini, Mondelli, Nasini and Hesse, 1970; Merlini, Nasini and Haddock, 1972; Phillipson, Hemingway and Ridsdale, 1978).

Stem : tetrahydroalstonine and/its N-oxide, akuammigine, 4-R-akuammigine N-oxide, 4-S-akuammigine N-oxide, dihydrocorynantheine, gambirdine, isogambirdine, roxburghine B, roxburghine D, roxburghine E, mitraphylline
(Chan, 1968; Merlini, Mondelli, Nasini and Hesse, 1970; Merlini, Nasini and Haddock, 1972; Phillipson, Hemingway and Ridsdale, 1978).

U. glabrata (Bl.) DC. from Sumatra, Indonesia.

Leaf : isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide.

Stem : speciophylline
(Phillipson, Hemingway and Ridsdale, 1978).

U. glabrescens Merr. et Perry from Solomon Islands.

Leaf : akuammigine, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide
(Phillipson, Hemingway and Ridsdale, 1978).

U. guianensis (Aubl.) Gmel. from Bolivia, Brazil, Guyana, South America, Venezuela.

Leaf : dihydrocorynantheine, hirsutine, hirsuteine, angustine, angustoline, isomitraphylline and its N-oxide, mitraphylline and its N-oxide, isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide.

Stem : dihydrocorynantheine, hirsutine, hirsuteine, angustine, angustoline, mitraphylline, isorhynchophylline, rhynchophylline and its N-oxide.

Flower : same as in the stem
(Phillipson and Hemingway, 1974; Phillipson, Hemingway and Ridsdale, 1978).

U. halleri Korth. from East Malaysia, Sandakan.

Leaf : isorhynchophylline, rhynchophylline
(Phillipson, Hemingway and Ridsdale, 1978).

U. homomalla Miq. from Laos, Thailand and Vietnam.

Leaf : 3-isoajmalicine, angustine, angustoline, angustidine, isomitraphylline, mitraphylline, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide
(Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974; Ponglux, Tantivatana and Pummangura, 1977; Phillipson, Hemingway and Ridsdale, 1978).

Stem : same as in the leaves, with the exception of mitraphylline
(Phillipson, Hemingway and Ridsdale, 1978).

U. hookeri Val. from Philippines.

Leaf : isomitraphylline, mitraphylline and its N-oxide,

isopteropodine, pteropodine, speciophylline, uncarine F
(Phillipson, Hemingway and Ridsdale, 1978).

U. jasminiflora Hook. f. from Malaysia.

Leaf : dihydrocorynantheine, gambirine, isomitraphylline, mitraphylline, isorhynchophylline, rhynchophylline
(Phillipson, Hemingway and Ridsdale, 1978).

U. kawakamii Havata from Philippines.

Leaf : isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide
(Phillipson, Hemingway and Ridsdale, 1978).

Stem, bark, root : mitraphylline, uncarine A, uncarine B
(Chan, Morsingh and Yeoh, 1966).

U. korrensis Kanehira from Caroline Island.

Leaf : isomitraphylline and its N-oxide, mitraphylline and its N-oxide, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide
(Phillipson, Hemingway and Ridsdale, 1978).

U. kunstleri King from Malaysia, Indonesia.

Leaf : hirsutine, isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide, corynoxine, corynoxine B
(Phillipson, Hemingway and Ridsdale, 1978).

U. laevifolia Elm. from Philippines.

Leaf : isomitraphylline, mitraphylline, isopteropodine, pteropodine, speciophylline, uncarine F (Phillipson, Hemingway and Ridsdale, 1978).

U. laevigata Wall. from Assam, India.

Leaf : isomitraphylline and its N-oxide, mitraphylline and its N-oxide, isopteropodine, speciophylline, uncarine A, uncarine B (Phillipson, Hemingway and Ridsdale, 1978).

U. lancifolia Hutch. from South China.

Leaf : isomitraphylline, mitraphylline and its N-oxide (Phillipson, Hemingway and Ridsdale, 1978).

U. lanosa Wall. from Malaysia.

Leaf : isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide (Phillipson, Hemingway and Ridsdale, 1978).

U. lobbii Hook. f. from Singapore.

Leaf : isopteropodine, pteropodine, speciophylline and its N-oxide, uncarine F (Phillipson, Hemingway and Ridsdale, 1978).

U. longiflora (Poir.) Merr. from Indonesia.

Leaf : isomitraphylline and its N-oxide, mitraphylline and its N-oxide, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide, isorhynchophylline and its N-oxide, rhynchophylline, isocorynoxeine or corynoxine, corynoxeine or corynoxine B.

Stem : isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide (Phillipson and Hemingway, 1973 b; Phillipson, Hemingway and Ridsdale, 1978).

U. macrophylla Wall. from Assam, India; Xieng Khouang Province, Laos; Yunnan Province, China.

Leaf : isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide, corynoxine, corynoxine B (Phillipson and Hemingway, 1973 c; Phillipson, Hemingway and Ridsdale, 1978).

Stem : same as in the leaves (Phillipson, Hemingway and Ridsdale, 1978).

U. orientalis Guill. from New Guinea, Solomon Islands.

Leaf : ajmalicine, 3-isoajmalicine, 19-epi-3-isoajmalicine, akuammigine, harmane, isomitraphylline and its N-oxide, mitraphylline and its N-oxide, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide.

Stem : harmane.

Flower : isopteropodine, pteropodine, speciophylline (Phillipson and Hemingway, 1975 b; Croquelois, Miet and Poisson, 1977; Phillipson, Hemingway and Ridsdale, 1978).

U. ovata Hook. f. from East Malaysia, Sarawak.

Leaf : harmane
(Phillipson, Hemingway and Ridsdale, 1978).

U. parviflora Ridl. from West Malaysia.

Leaf : angustine, angustoline, angustidine, isomitraphylline and its N-oxide, mitraphylline and its N-oxide, isopteropodine, pteropodine, speciophylline, uncarine F.

Stem : angustine, angustoline, angustidine, isomitraphylline, mitraphylline
(Phillipson, Hemingway and Ridsdale, 1978).

U. pedicellata Roxb. from West Java, Indonesia.

Leaf : isorhynchophylline, rhynchophylline, corynoxine, corynoxine B
(Phillipson, Hemingway and Ridsdale, 1978).

U. perrottetii (A. Rich.) Merr. from Philippines.

Leaf : isomitraphylline and its N-oxide, mitraphylline and its N-oxide, isopteropodine, pteropodine, speciophylline, uncarine F
(Phillipson, Hemingway and Ridsdale, 1978).

U. philippinensis Elm. from Philippines.

Leaf : isopteropodine, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide
(Phillipson, Hemingway and Ridsdale, 1978).

U. pilosa Roxb. from Assam, India.

Leaf : isomitraphylline and its N-oxide, mitraphylline and its N-oxide, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F (Phillipson, Hemingway and Ridsdale, 1978).

U. pteropoda Miq. from Malaysia, Singapore.

Leaf : isomitraphylline and its N-oxide, mitraphylline and its N-oxide, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide, isocorynoxeine, corynoxeine (Phillipson, Hemingway and Ridsdale, 1978).

Stem : isopteropodine, pteropodine.

Stem bark : same as in the stem.

Root : same as in the stem (Chan, Morsingh and Yeoh, 1966; Yeoh, Chan and Morsingh, 1966).

U. quadrangularis Geddes from Thailand.

Leaf : isomitraphylline, mitraphylline.

Stem bark : isopteropodine, pteropodine (Tantivatana, Ponglux, Jirawongse and Silpvisavanont, 1979).

U. rhynchophylla Miq. from China, Japan.

Leaf : angustine, angustoline, angustidine, isorhynchophylline, rhynchophylline and its N-oxide, isocorynoxeine, corynoxeine (Aimi, Yamanaka, Endo, Sakai and Haginiwa, 1972; Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974; Aimi, Yamanaka, Shinma, Fujiu, Kurita, Sakai and Haginiwa, 1977; Phillipson, Hemingway and Ridsdale, 1978).

Stem and Root : dihydrocorynantheine, corynantheine, hirsutine, hirsuteine, isorhynchophylline, rhynchophylline, isocorynoxeine, corynoxeine (Phillipson, Hemingway and Ridsdale, 1978).

Hook : isorhynchophylline, rhynchophylline (Saxton, 1965 a).

Whole plant : akuammigine, dihydrocorynantheine, corynantheine, hirsutine, hirsuteine, geissoschizine methyl ether, isocorynoxeine, corynoxeine (Aimi, Yamanaka, Endo, Sakai and Haginiwa, 1972; Ban, Seto and Oishi, 1975; Aimi, Yamanaka, Shinma, Fujiu, Kurita, Sakai and Haginiwa, 1977).

U. rhynchophylla Miq. var. *kouteng* Yamazaki from China.

Leaf : angustine, angustoline, angustidine, isorhynchophylline and its N-oxide, rhynchophylline, isocorynoxeine, corynoxeine (Phillipson, Hemingway and Ridsdale, 1978).

U. rostrata Pierre ex Pitard from Vietnam.

Leaf : 3-isoajmalicine, akuammigine, roxburghine D (Phillipson, Hemingway and Ridsdale, 1978).

U. roxburghiana Korth. from Malaysia, Sumatra, Indonesia.

Leaf : isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F.

Stem : same as in the leaves, with the exception of pteropodine N-oxide
(Phillipson, Hemingway and Ridsdale, 1978).

U. sclerophylla Havil. from Singapore.

Leaf : dihydrocorynantheine, isorhynchophylline, rhynchophylline
(Phillipson, Hemingway and Ridsdale, 1978).

U. sessilifructus Roxb. from Assam and Calcutta, India.

Leaf : 3-isoajmalicine, 19-epi-3-isoajmalicine, akuammigine, hirsutine, isomitraphylline and its N-oxide, mitraphylline and its N-oxide, uncarine F, uncarine A, uncarine B, isorhynchophylline, rhynchophylline, corynoxine, corynoxine B
(Phillipson, Hemingway and Ridsdale, 1978).

U. setiloba Benth. from Moluccas, Philippines.

Leaf : isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide.

Stem : same as in the leaves
(Phillipson, Hemingway and Ridsdale, 1978).

U. sinensis (Oliv.) Havil. from North Vietnam, South China.

Leaf : akuammigine, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide.

Fruit and seed : same as in the leaves (Phillipson, Hemingway and Ridsdale, 1978).

U. sterrophylla Merr. et Perry from New Guinea.

Leaf : 3-isoajmalicine, isomitraphylline, mitraphylline, isopteropodine, pteropodine, speciophylline and its N-oxide, uncarine F, isorhynchophylline, rhynchophylline.

Stem : isopteropodine, pteropodine, speciophylline, isorhynchophylline, rhynchophylline.

Stem bark : isopteropodine, pteropodine, speciophylline, uncarine F.

Stem wood : isorhynchophylline, rhynchophylline (Phillipson, Hemingway and Ridsdale, 1978).

U. tomentosa DC. from South America, West India.

Leaf : dihydrocorynantheine and its N-oxide, hirsutine and its N-oxide, hirsuteine, isomitraphylline and its N-oxide, mitraphylline, isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide, rotundifoline, isorotundifoline.

Stem : same as in the leaves (Hemingway and Phillipson, 1974).

Flower : dihydrocorynantheine, hirsutine, hirsuteine, isomitraphylline, mitraphylline, isorhynchophylline and its N-oxide, rhynchophylline and its N-oxide, rotundifoline, isorotundifoline (Phillipson, Hemingway and Ridsdale, 1978).

U. tonkinensis Havil. from North Vietnam.

Leaf : angustine, angustoline, angustidine (Phillipson, Hemingway and Ridsdale, 1978).

U. toppingii Merr. from Philippines.

Leaf : isomitraphylline and its N-oxide, mitraphylline and its N-oxide, isopteropodine and its N-oxide, pteropodine, speciophylline and its N-oxide, uncarine F.

Flower : isomitraphylline, mitraphylline, isopteropodine, pteropodine, speciophylline, uncarine F.

Stem : isomitraphylline, mitraphylline, isopteropodine, pteropodine (Phillipson, Hemingway and Ridsdale, 1978).

U. valetoniana Merr. et Perry from New Guinea.

Leaf : dihydrocorynantheine, hirsutine, hirsuteine (Phillipson, Hemingway and Ridsdale, 1978).

U. velutina Havil. from Philippines.

Leaf : isomitraphylline, mitraphylline, isopteropodine and its N-oxide, pteropodine and its N-oxide, speciophylline and its N-oxide, uncarine F and its N-oxide (Phillipson and Hemingway, 1975 b; Phillipson, Hemingway and Ridsdale, 1978).

3. Other botanical sources of *Uncaria* indole and oxindole alkaloids

Many of *Uncaria* indole and oxindole alkaloids have been isolated from other genera, they are summarised as follow :-

a. Indole alkaloids

1. Pentacyclic heteroyohimbines

ajmalicine : *Corynanthe yohimbe* K. Schum.
: *Lochnera lancea* (Boj. ex A. DC.) K. Schum. (Saxton, 1960).
: *Mitragyna javanica* var. *microphylla* Koord and Valeton (Shellard, Beckett, Tantivatana, Phillipson and Lee, 1967).
: *M. speciosa* Korth. (Beckett, Shellard, Phillipson and Lee, 1966 b; Shellard, Houghton and Resha, 1978 a).
: *Rauvolfia affinis* Muell. Arg.
: *R. beddomei* Hook. f.
: *R. canescens* L.
: *R. fruticosa* Burck
: *R. heterophylla* Roem. et Schult.
: *R. inebrians* K. Schum.
: *R. javanica* Koord et Val. (Schlittler, 1965).

: *Rauvolfia ligustrina* Roem. et Schult.
(Muller, 1957).
: *R. micrantha* Hook. f.
: *R. nitida* Jacq.
: *R. pentaphylla* Ducke
: *R. rosea* K. Schum.
: *R. sellowii* Muell. Arg.
(Schlittler, 1965).
: *R. serpentina* (L.) Benth. ex Kurz.
(Bently, 1950).
: *R. sumatrana* (Miq.) Jack.
(Schlittler, 1965).
: *R. verticellata* (Lour.) Baill.
(Saxton, 1960)
: *R. viridis* (Muell. Arg.) Guillaumin
: *R. vomitoria* Afz.
(Schlittler, 1965).
: *Vinca rosea* L.
(Saxton, 1960).

3-isoajmalicine : *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard, Phillipson and Gupta, 1969 b).
: *M. rotundifolia* (Roxb.) O. Kuntze
(Houghton and Shellard, 1974).
: *M. speciosa* Korth.
(Shellard, Houghton and Resha, 1978 b).

tetrahydroalstonine : *Alstonia constricta* F. Muell.
(Saxton, 1965 b).
: *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard and Houghton, 1971).
: *Rauvolfia lingustrina* Roem. et Schult.
(Muller, 1957).
: *R. sellowii* Muell. Arg.
(Hochstein, 1955).
: *Vinca lancea* Boj. ex A. DC.
: *V. rosea* L.
(Saxton, 1965 b).

rauniticine : *Rauvolfia nitida* Jacq.
(Salkin, Hosansky and Jaret, 1961).

akuammigine : *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard, Phillipson and Gupta, 1968 a).
: *M. speciosa* Korth.
(Shellard, Houghton and Resha, 1978 b).
: *Picralima nitida* Stapf, Th. and H. Durand.
(*P. klaineana* Pierre).
(Henry, 1932; Robinson and Thomas, 1954).

akuammigine N-oxide : *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard and Houghton, 1973).

2. Tetracyclic heteroyohimbines

dihydrocorynantheine : *Corynanthe yohimbe* K. Schum.
(Karrer, Schwyzer and Flam, 1952)

: *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard, Phillipson and Gupta, 1969 a; Shellard and Houghton, 1972 b).

: *Pseudocinchona africana* Aug. Chev.
(Cu, Goutarel and Janot, 1957).

corynantheine : *Corynanthe yohimbe* K. Schum.
(Karrer and Salomon, 1926).

: *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard and Houghton, 1972 d).

: *Pseudocinchona africana* Aug. Chev.
(Cu, Goutarel and Janot, 1957).

hirsutine : *Mitragyna hirsuta* Havil.
(Shellard, Tantivatana and Beckett, 1967).

: *M. parvifolia* (Roxb.) Korth.
(Shellard, Phillipson and Gupta, 1969 a; Shellard and Houghton, 1972 b).

: *M. rubrostipulata* (Schum.) Havil.
(Shellard and Lala, 1978).

: *M. stipulosa* (DC.) O. Kuntze
(Houghton, Lala, Shellard and Sarpong, 1976).

: *M. tubulosa* Havil.
(Rungsiyakul, 1973).

hirsuteine : *Mitragyna hirsuta* Havil.
(Phillipson, Tantivatana, Tarpo and Shellard, 1973).

: *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard and Houghton, 1972 c).
: *M. rubrostipulata* (Schum.) Havil.
(Shellard and Lala, 1978).

3. Other indole alkaloids.

angustine : *Mitragyna javanica* Koord. et Val.
: *M. parvifolia* (Roxb.) Korth.
: *Nauclea coadunata* Roxb. ex J. E. Smith
: *Strychnos angolensis* Gilg
(Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974).
: *S. angustiflora* Benth.
(Au, Cheung and Sternhell, 1973).
: *S. borneensis* Leenh.
: *S. camptoneura* Gilg et Busse.
: *S. floribunda* Gilg
: *S. ledermannii* Gilg et Bended
: *S. minor* Dennst
: *S. odorata* A. Chev.
: *S. ovata* A. W. Hill
: *S. potatorum* L. f.
: *S. samba* Duvign
: *S. scheffleri* Gilg
: *S. trichoneura* Leeuwenberg
: *S. umbellata* (Lour.) Merr.

: *Strychnos usambarensis* Gilg

: *S. vanprukii* Craib

: *S. xantha* Leeuwenberg

(Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974).

angustoline : *Strychnos angustiflora* Benth.

(Au, Cheung and Sternhell, 1973).

: *S. borneensis* Leenh.

: *S. minor* Dennst.

: *S. odorata* A. Chev.

: *S. ovata* A. W. Hill

: *S. samba* Duvign

: *S. scheffleri* Gilg

: *S. trichoneura* Leeuwenberg

: *S. umbellata* (Lour.) Merr.

: *S. vanprukii* Craib

: *S. xantha* Leeuwenberg

(Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974).

angustidine : *Strychnos angolensis* Gilg

: *S. angustiflora* Benth.

: *S. borneensis* Leenh.

: *S. minor* Dennst.

: *S. odorata* A. Chev.

: *S. ovata* A. W. Hill

: *Strychnos samba* Duvign

: *S. scheffleri* Gilg

: *S. trichoneura* Leeuwenberg

: *S. umbellata* (Lour.) Merr.

: *S. vanprukii* Craib

: *S. xantha* Leeuwenberg

(Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974).

yohimbine : *Alchorea floribunda* Muell. Arg.

: *Aspidosperma quebracho-blanco* Schlecht.

: *Corynanthe macroceras* K. Schum.

: *C. paniculata* Welw.

: *C. yohimbe* K. Schum.

: *Diphlorhynchus condylocarpon* Pich.

: *Hunteria eburnea* Pich.

: *Lochnera lancea* K. Schum.

: *Pausinystalia trillesii* Beille

: *Rauvolfia canescens* L.

: *R. heterophylla* Willd. ex Roem. et Schult.

: *R. ligustrina* Roem. et Schult.

: *R. serpentina* (L.) Benth. ex Kurz

: *R. sumatrana* (Miq.) Jack.

: *R. vomitoria* Afzel.

(Saxton, 1960; Schlittler, 1965; Manske, 1965).

β-yohimbine : *Amsonia elliptica* Roem. et Schult.
: *Aspidosperma oblongum* A. DC.
: *A. quebracho-blanco* Schlecht.
: *Corynanthe paniculata* Welw.
: *C. yohimbe* K. Schum.
: *Diplorhynchus condylocarpon* Pich.
: *Rauvolfia canescens* L.
(Saxton, 1960; Schittler, 1965, Manske, 1965).

corynanthine : *Pseudocinchona africana* A. Chev.
(Manske, 1965).

pseudoyohimbine : *Corynanthe yohimbe* K. Schum.
(Manske, 1965)

alloyohimbine : *Corynanthe yohimbe* K. Schum.
(Manske, 1965).

α-yohimbine : *Alstonia constricta* F. v. Muell.
: *Corynanthe yohimbe* K. Schum.
: *Pseudocinchona africana* A. Chev.
: *Rauvolfia canescens* L.
: *R. hirsuta* Jacq.
: *R. heterophylla* Roem. et Schult.
: *R. ligustrina* Roem. et Schult.
: *R. sumatrana* (Miq.) Jack.
: *R. vomitoria* Afz.
(Saxton, 1960; Schlittler, 1965; Manske, 1965).

3-epi-α-yohimbine : *Rauvolfia serpentina* (L.) Benth. ex Kurz
(Manske, 1965).

b. Oxindole alkaloids.

1. Pentacyclic oxindoles

isomitraphylline : *Mitragyna hirsuta* Havil.
(Shellard, Tantivatana and Beckett, 1967).
: *M. javanica* Koord. et Val. var. *microphylla* Koord. et Val.
(Shellard, Beckett and Tantivatana, 1967).
: *M. parvifolia* (Roxb.) Korth.
(Shellard, Phillipson and Gupta, 1969 b).
: *M. rotundifolia* (Roxb.) O. Kuntze
(Houghton and Shellard, 1974).
: *M. rubrostipulata* (Schum.) Havil.
(Shellard and Lala, 1978).
: *M. speciosa* Korth.
(Beckett, Shellard, Phillipson and Lee, 1966 a; Shellard, Houghton and Resha, 1978 a).
: *M. tubulosa* Havil.
(Shellard and Rungsiyakul, 1973).

mitraphylline : *Mitragyna hirsuta* Havil.
(Shellard, Tantivatana and Beckett, 1967).
: *M. javanica* Koord. et Val. var. *microphylla* Koord. et Val.
(Shellard, Beckett and Tantivatana, 1967).

: *M. parvifolia* (Roxb.) Korth.
(Shellard, Phillipson and Gupta, 1969 b;
Shellard and Houghton, 1972 b).

: *M. rotundifolia* (Roxb.) O. Kuntze
(Houghton and Shellard, 1974).

: *M. rubrostipulacea* Havil.
(Seaton, Tondeur and Marion, 1958).

: *M. rubrostipulata* (Schum.) Havil.
(Shellard and Lala, 1978).

: *M. speciosa* Korth.
(Beckett, Shellard, Phillipson and Lala, 1966 a;
Shellard, Houghton and Resha, 1978 a).

: *M. stipulosa* (DC.) O. Kuntze
(Beckett, Shellard and Tackie, 1963; Houghton,
Lala, Shellard and Sarpong, 1976 a).

: *M. tubulosa* Havil.
(Shellard and Rungsiyakul, 1973).

isopteropodine : *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard, Phillipson and Gupta, 1968 a).

pteropodine : *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard, Phillipson and Gupta, 1968 a).

speciophylline : *Mitragyna inermis* (Willd.) O. Kuntze
(Shellard and Sarpong, 1969; Shellard and
Sarpong, 1970).

: *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard, Phillipson and Gupta, 1968 a).
: *M. speciosa* Korth.
(Beckett, Shellard, Phillipson and Lee, 1965;
Beckett, Shellard, Phillipson and Lee 1966 a;
Shellard, Houghton and Resha, 1978 a).

speciophylline N-oxide : *Mitragyna parvifolia* (Roxb.) Korth.
(Rungsiyakul, 1973).

uncarine F : *Mitragyna inermis* (Willd) O. Kuntze
(Shellard and Sarpong, 1969; Shellard and Sarpong, 1970).
: *M. parvifolia* (Roxb.) Korth.
(Shellard, Phillipson and Gupta, 1968 a).

uncarine F N-oxide : *Mitragyna parvifolia* (Roxb.) Korth.
(Rungsiyakul, 1973).

2. Tetracyclic oxindoles

isorhynchophylline : *Mitragyna ciliata* Aubr. et Pellegr.
(Beckett, Shellard and Tackie, 1963 b;
Shellard and Sarpong, 1970).
: *M. hirsuta* Havil.
(Shellard, Tantivatana and Beckett, 1967).
: *M. inermis* (Willd.) O. Kuntze
(Shellard and Sarpong, 1969; Shellard and Sarpong, 1970).

: *Mitragyna parvifolia* (Roxb.) Korth.

(Shellard and Phillipson, 1964 b; Shellard, Phillipson and Gupta, 1968 a; Shellard and Houghton, 1972 b).

: *M. rubrostipulata* (Schum.) Havil.

(Shellard and Lala, 1978).

: *M. rotundifolia* (Roxb.) O. Kuntze

(Shellard and Phillipson, 1964 a; Houghton and Shellard, 1974).

: *M. speciosa* Korth.

(Shellard, Houghton and Resha, 1978 a).

: *M. stipulosa* (DC.) O. Kuntze

(Beckett, Shellard and Tackie, 1963 a; Houghton, Lala, Shellard and Sarpong, 1976).

: *M. tubulosa* Havil.

(Shellard and Rungsiyakul, 1973).

isorhynchophylline N-oxide : *Mitragyna inermis* (Willd.) O. Kuntze

(Shellard, Phillipson and Sarpong, 1971).

: *M. rotundifolia* (Roxb.) O. Kuntze

(Shellard, Phillipson and Sarpong, 1971).

isocorynoxeine : *Mitragyna rotundifolia* (Roxb.) O. Kuntze

(Houghton and Shellard, 1974).

corynoxeine : *Mitragyna hirsuta* Havil.

(Rungsiyakul, 1973).

: *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard and Houghton, 1972 c).

: *M. rotundifolia* (Roxb.) O. Kuntze
(Houghton and Shellard, 1974).

: *M. speciosa* Korth.
(Shellard, Houghton and Resha, 1978 a).

: *M. stipulosa* (DC.) O. Kuntze
(Houghton, Lala and Sarpong, 1976).

: *Pseudocinchona africana* Aug. Chev.
(Cu, Goutarel and Janot, 1957).

rhynchophylline : *Adina rubrostipulata* K. Schum.
(Seaton, Nair, Edwards and Marion, 1960).

: *Mitragyna ciliata* Aubr. et Pellegr.
(Beckett, Shellard and Tackie, 1963 b; Shellard and Sarpong, 1970).

: *M. hirsuta* Havil.
(Shellard, Tantivatana and Beckett, 1967).

: *M. inermis* (Willd.) O. Kuntze
(Shellard and Sarpong, 1969; Shellard and Sarpong, 1970).

: *M. parvifolia* (Roxb.) Korth.
(Shellard and Phillipson, 1964 b; Shellard, Phillipson and Gupta, 1968 a; Shellard and Houghton, 1972 b).

: *Mitragyna rubrostipulata* (Schum.) Havil. (Hendrickson and Sims, 1963; Shellard and Lala, 1978).

: *M. rotundifolia* (Roxb.) O. Kuntze (Barger, Dyer and Sargent, 1939; Houghton and Shellard, 1974).

: *M. speciosa* Korth. (Shellard, Houghton and Resha, 1978 a).

: *M. stipulosa* (DC.) O. Kuntze (Beckett, Shellard and Tackie, 1963 a; Houghton, Lala, Shellard and Sarpong, 1976).

: *M. tubulosa* Havil. (Shellard and Rungsiyakul, 1973).

rhynchophylline N-oxide : *Mitragyna inermis* (Willd.) O. Kuntze (Shellard, Phillipson and Sarpong, 1971).

: *M. rotundifolia* (Roxb.) O. Kuntze (Shellard and Phillipson, 1964 a; Shellard, Phillipson and Sarpong, 1971).

: *M. rubrostipulata* (Schum.) Havil. (Shellard and Lala, 1978).

rotundifoline : *Mitragyna ciliata* Aubr. et Pellegr. (Beckett, Shellard and Tackie, 1963 b; Shellard and Sarpong, 1970).

: *M. inermis* (Willd.) O. Kuntze (Shellard and Sarpong, 1969).

: *Mitragyna parvifolia* (Roxb.) Korth.
(Shellard and Phillipson, 1964 b; Shellard, Phillipson and Gupta, 1968 a).

: *M. rotundifolia* (Roxb.) O. Kuntze
(Barger, Dyer and Sargent, 1939).

: *M. rubrostipulata* (Schum.) Havil.
(Shellard and Lala, 1978).

: *M. stipulosa* (DC.) O. Kuntze
(Shellard and Sarpong, 1970).

: *M. tubulosa* Havil.
(Shellard and Rungsiyakul, 1973).

isorotundifoline : *Mitragyna ciliata* Aubr. et Pellegr.
(Beckett, Shellard and Tackie, 1963 b; Shellard and Sarpong, 1970).

: *M. inermis* (Willd.) O. Kuntze
(Shellard and Sarpong, 1969; Shellard and Sarpong, 1970).

: *M. parvifolia* (Roxb.) Korth.
(Shellard and Phillipson, 1964 b; Shellard, Phillipson and Gupta, 1968 a).

: *M. rubrostipulata* (Schum.) Havil.
(Shellard and Lala, 1978).

: *M. stipulosa* (DC.) O. Kuntze
(Beckett, Shellard and Tackie, 1963 a).

: *M. tubulosa* Havil.
(Shellard and Rungsiyakul, 1973).

speciofoline : *Mitragyna speciosa* Korth.
(Beckett, Shellard and Tackie, 1965;
Hemingway, Houghton, Phillipson and Shellard,
1975; Shellard, Houghton and Resha, 1978 a).

corynoxine : *Mitragyna speciosa* Korth.
(Shellard, Houghton and Resha, 1978 a).
: *Pseudocinchona africana* Aug. Chev.
(Cu, Goutarel and Janot, 1957).

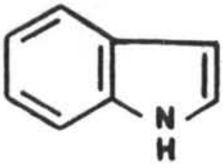
corynoxine B : *Mitragyna speciosa* Korth.
(Shellard, Houghton and Resha, 1978 a).

Chemical nature of alkaloids

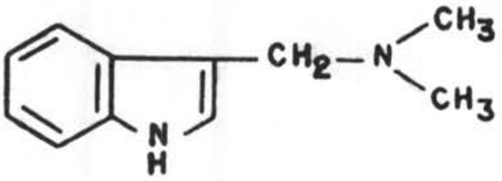
The beginning of alkaloid chemistry is dated back about 170 years when F. W. Sertürner announced the isolation of morphine in 1805. Later, Gomes obtained a crystalline precipitate, "cinchonino', from cinchona bark in 1810. Subsequently, P. J. Pelletier and J. B. Caventou (1820) separated two new alkaloids quinine and cinchonine from the mixture "cinchonino". The investigations of alkaloids were intensified between 1820-1850 and a large number of alkaloids were isolated and characterised (Pelletier, 1969).

To establish an absolute chemical structure of a pure alkaloid, the molecular formula has to be determined firstly. This can nowadays be obtained easily by high resolution mass spectrometry. The functions of oxygen and nitrogen atoms in the molecule are next to be ascertained by using standard chemical reactions and, more modernly, by spectroscopic means, i.e. ultraviolet, infrared and nuclear magnetic resonance.

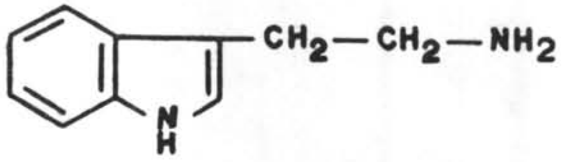
A great number of alkaloids having indole nucleus (1) are found to occur in plants. The majority of them have quite complex structures with only a few as simple derivatives; e.g. gramine (2) and tryptamine (3).



(1)



(2)



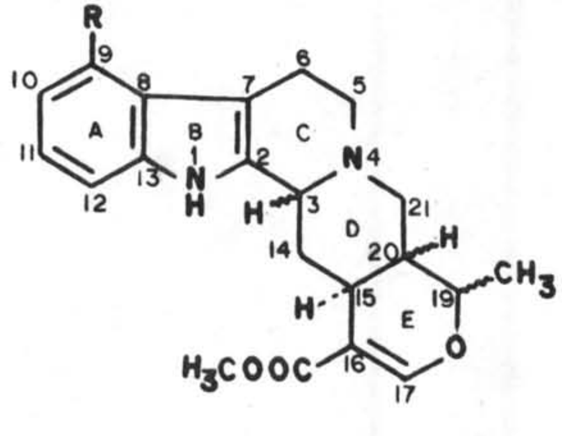
(3)

Alkaloids have been obtained from a number of *Uncaria* species and most of them are of the pentacyclic and tetracyclic heteroyohimbine-types and the corresponding oxindoles. Harmane, pyridino-indoloquinolizidinones, roxburghines and yohimbines are examples of the minor alkaloids.

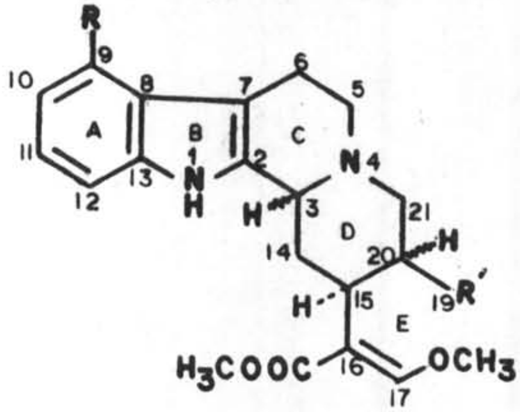
1. Basic structures of indole alkaloids.

There are two types of heteroyohimbine alkaloids depending upon the nature of ring E. Their basic structures are illustrated below :-

a. Pentacyclic heteroyohimbines (Closed E ring)

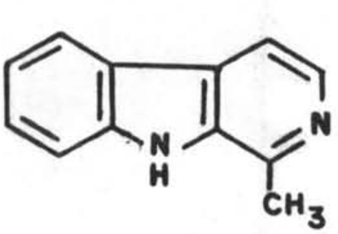


b. Tetracyclic heteroyohimbines (Open E ring or E-*seco*)

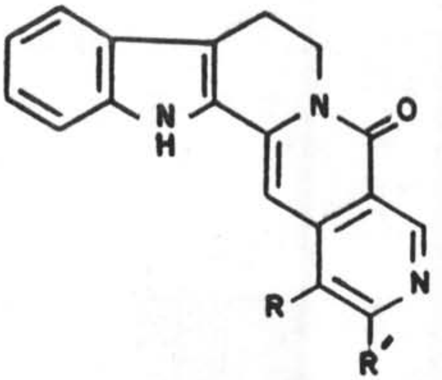


c. Other indole alkaloids.

Harmane



Pyridino-indolo-quinolizidinones

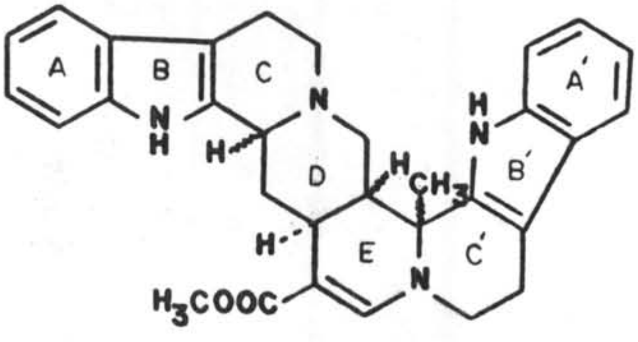


Angustine, R = $-CH = CH_2$; R' = H

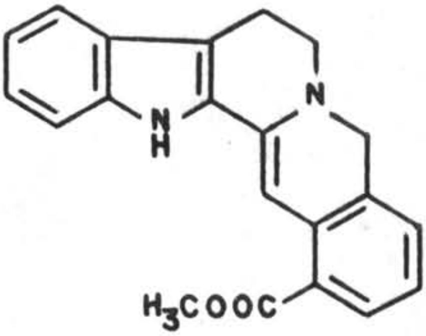
Angustoline, R = $-CH(OH)CH_3$; R' = H

Angustidine, R = H ; R' = $-CH_3$

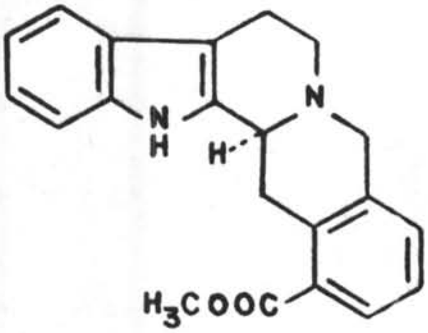
Roxburghines



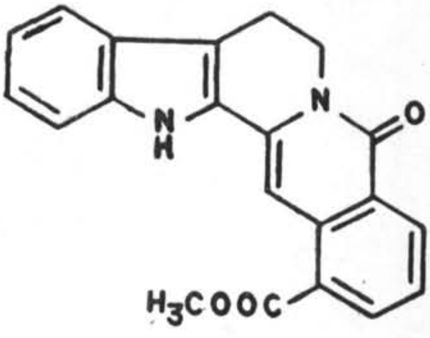
Gambirtannine



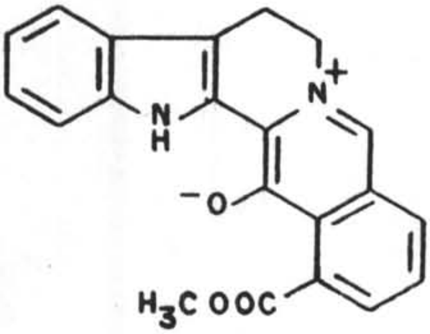
Dihydrogambirtannine



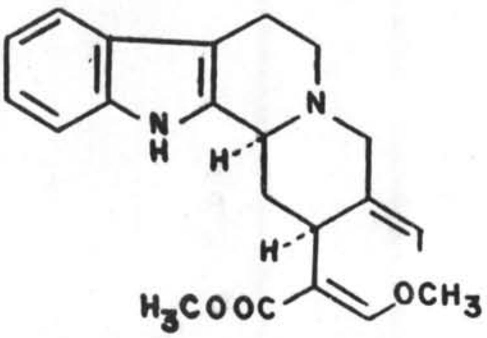
Oxygambirtannine



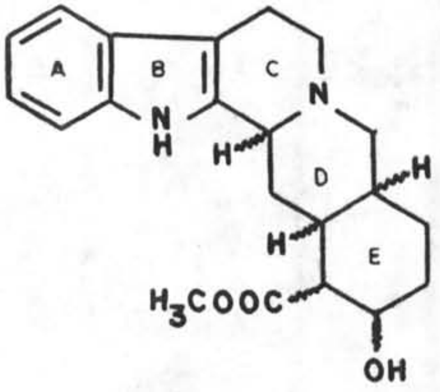
Neooxygambirtannine



Geissoschizine methyl ether



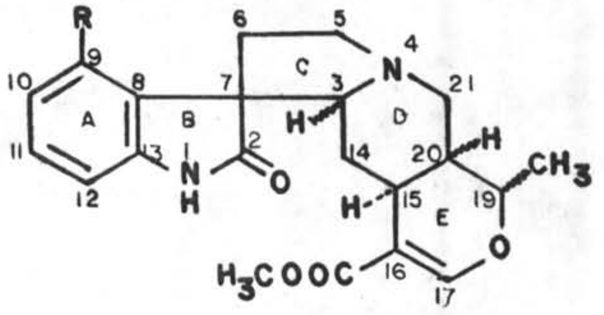
Yohimbine and its isomers



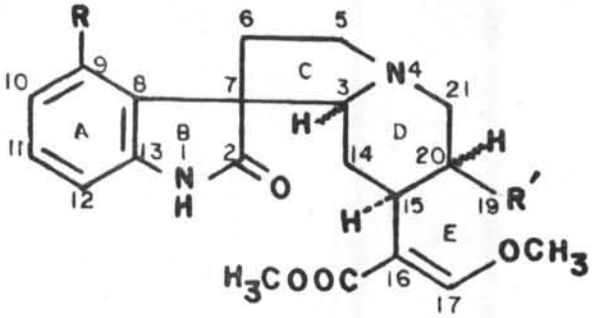
2. Basic structures of oxindole alkaloids.

There are also two types of oxindole alkaloids depending upon the nature of ring E.

a. Pentacyclic oxindoles (Closed E ring)

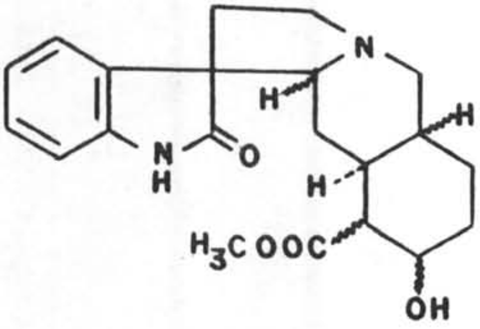


b. Tetracyclic oxindoles (Open E-ring or E-*seco*)

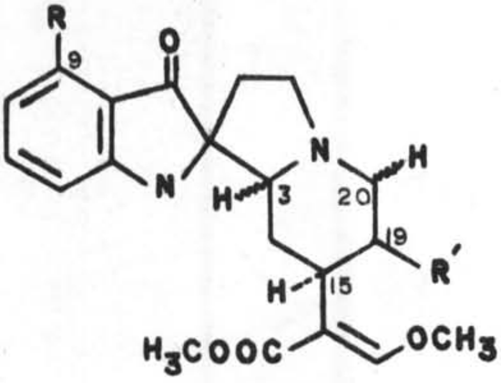


c. Other oxindole alkaloids

Yohimbine oxindole



Tetracyclic pseudoindoxyl



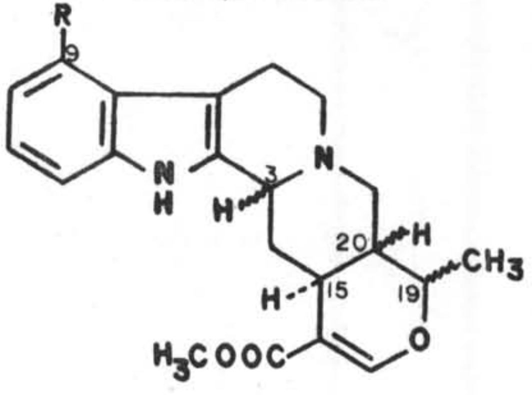
3. Configurations of indole alkaloids.

Since all known heteroyohimbine alkaloids possess a C(15)-Hα configuration and have asymmetric centres at C(3) and C(20), there are thus four possible configurations :-

Configuration	C(3)-H	C(20)-H
normal	α	β
pseudo	β	β
allo	α	α
epiallo	β	α

The pentacyclic heteroyohimbines have another asymmetric centre at C(19), i.e. CH_3α or β, so that eight isomers are possible (Phillipson and Shellard, 1967). The tetracyclic heteroyohimbines may show geometric isomerisation because of the double bond between C(16) and C(17) though all the alkaloids of known absolute configuration possess a C(17)-H *cis* to the ester group on C(16) (Shellard, Phillipson and Gupta, 1969 b). The aromatic substitution (R) have been found to occur at C(9), the group being either an hydroxy or a methoxy group. In the tetracyclic heteroyohimbines (R') may be either an ethyl (CH_2-CH_3) or a vinyl (CH=CH_2) group.

a. Pentacyclic heteroyohimbines



Alkaloid	Configuration	C(9)-R	C(19)-CH_3
ajmalicine	*normal*	H	α
3-isoajmalicine	*pseudo*	H	α
tetrahydroalstonine*	*allo*	H	α
akuammigine*	*epiallo*	H	α
19-epi-ajmalicine	*normal*	H	β
19-epi-3-isoajmalicine	*pseudo*	H	β
rauniticine	*allo*	H	β
3-isorauniticine	*epiallo*	H	β
14-hydroxy-3-isorauniticine	*epiallo*	H and C(14)H = OH	β
isomitrajavine**	*normal*	OCH_3	α
(mitrajavine)	*pseudo*	OCH_3	α

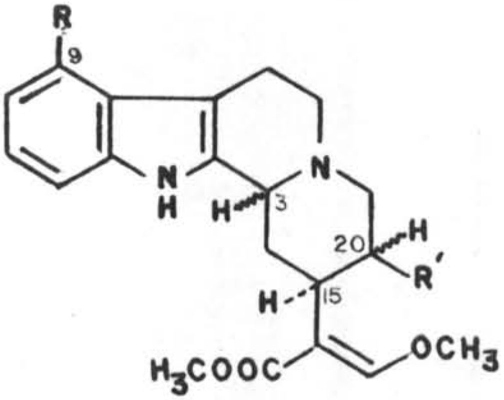
(Wenkert and Roychaudhuri, 1958; Shamma and Richey, 1963; Phillipson and Shellard, 1967; Shellard and Sarpong, 1971 b; Saxton, 1973; Phillipson and Hemingway, 1975 a; Supavita, 1979).

* = with its N-oxide

** = semi-synthetic, i.e. derived chemically from naturally occurring alkaloids.

( ) = not yet isolated from *Uncaria* species

b. Tetracyclic heteroyohimbines



Alkaloid	Configuration	C(9)-R	C(20)-R'
dihydrocorynantheine*	*normal*	H	CH_2-CH_3
hirsutine*	*pseudo*	H	CH_2-CH_3
(corynantheidine)	*allo*	H	CH_2-CH_3
(isocorynantheidine)	*epiallo*	H	CH_2-CH_3

Alkaloid	Configuration	C(9)-R	C(20)-R'
(corynantheine)	*normal*	H	$CH=CH_2$
hirsuteine	*pseudo*	H	$CH=CH_2$
epiallo-corynantheine	*epiallo*	H	$CH=CH_2$
gambirine	*normal*	OH	CH_2-CH_3
(isogambirine)	*pseudo*	OH	CH_2-CH_3
(speciogynine)	*normal*	OCH_3	CH_2-CH_3
(mitraciliatine)	*pseudo*	OCH_3	CH_2-CH_3
(mitragynine)	*allo*	OCH_3	CH_2-CH_3
(speciociliatine)	*epiallo*	OCH_3	CH_2-CH_3
(paynantheine)	*normal*	OCH_3	$CH=CH_2$
(isopaynantheine)	*pseudo*	OCH_3	$CH=CH_2$

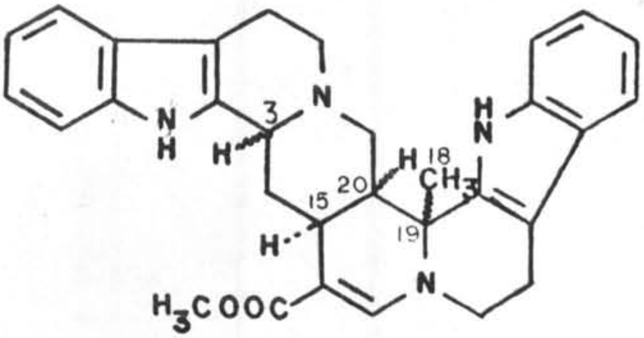
(Beckett, Shellard, Phillipson and Lee, 1966 b; Phillipson and Shellard, 1966; Phillipson and Shellard, 1967; Lee, Trager and Beckett, 1967; Saxton, 1968; Trager, Phillipson and Beckett, 1968; Phillipson and Hemingway, 1975 a; Shellard, Houghton and Resha, 1978 b).

* = with its N-oxide

( ) = not yet isolated from *Uncaria* species

c. Other indole alkaloids

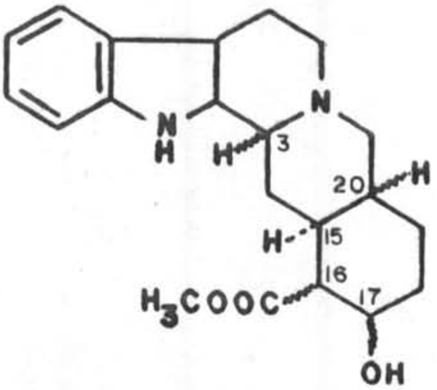
Roxburghines



Alkaloid	Configuration	C(18)
roxburghine B	*epiallo*	β
roxburghine C	*normal*	α
roxburghine D	*pseudo*	α
roxburghine E	*pseudo*	β

(Phillipson, Hemingway and Ridsdale, 1978).

Yohimbine and its isomers



All natural isomers of yohimbine posses at C915) the α configuration (Pelletier, 1969).

Alkaloid	Synonym	Configuration	C(16)	C(17)
yohimbine	quebrachine	*normal*	α	α
β-yohimbine	amsonine	*normal*	α	β
corynanthine	rauhimbine	*normal*	β	α
pseudoyohimbine	—	*pseudo*	α	α
epi-3-β-yohimbine	—	*pseudo*	α	β
epi-3-corynanthine	—	*pseudo*	β	α
alloyohimbine	—	*allo*	β	β
α-yohimbine	corynantheidine	*allo*	β	α
epi-3-alloyohimbine	—	*epiallo*	β	β
epi-3-α-yohimbine	epi-3-rauwolscine isorauhimbine	*epiallo*	β	α

(Shamma and Richey, 1963; Manske, 1965).

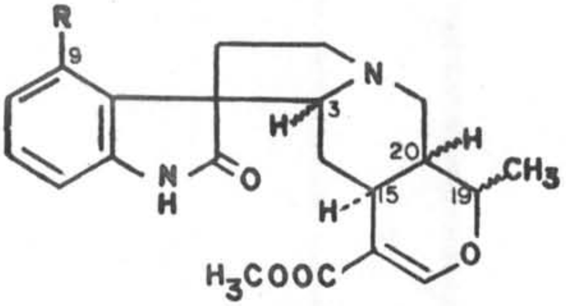
4. Configurations of oxindole alkaloids.

Configurations of oxindoles are similar to those of heteroyohimbines, thus, the four configurations are possible. In addition, the oxindoles have an asymmetric centre at C(7), those alkaloids in which the lactam carbonyl lies below the plane of the C/D-rings being termed the A series and those in which the lactam carbonyl lies above the plane of the C/D-rings being termed the B series (Finch and Taylor, 1962 a, b). Further, in both types of oxindoles the lone pair of electrons on N(4) may either be on the same side of the C(7) as the lactam carbonyl group or on the opposite side; the former are known as *syn* and the latter as *anti* alkaloids (Shamma, Shine, Kompis, Sticzay, Morsingh, Poisson and Pousset, 1967).

Configuration	C(3)-H	C(20)-H	C(7)/series
normal	α	β	A or B
pseudo	β	β	A or B
allo	α	α	A or B
epiallo	β	α	A or B

(Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968).

a. Pentacyclic oxindoles



Alkaloid	Configuration	C(7)/series	C(9)-R	C(19)-CH_3
isomitraphylline*	*normal*	A	H	α
mitraphylline*	*normal*	B	H	α
isopteropodine*	*allo*	A	H	α
pteropodine*	*allo*	B	H	α
speciophylline*	*epiallo*	A	H	α
uncarine F*	*epiallo*	B	H	α
uncarine A	*normal*	A	H	β
uncarine B	*normal*	B	H	β
(rauniticine oxindole A)	*allo*	A	H	β
(rauniticine oxindole B)	*allo*	B	H	β

Alkaloid	Configuration	C(7)/series	C(9)-R	$C(19)-CH_3$
(javaphylline)	*normal*	A	OCH_3	α
isojavaphylline**	*normal*	B	OCH_3	α

(Beckett, Shellard, Phillipson and Lee, 1966 a; Shamma, Shine, Kompis, Sticzay, Morsingh, Poisson and Pousset, 1967; Beecham, Hart, Johns and Lamberton, 1967 a; Shellard, Phillipson and Gupta, 1968 a; Saxton, 1973; Phillipson and Hemingway, 1975 a).

* = with its N-oxide

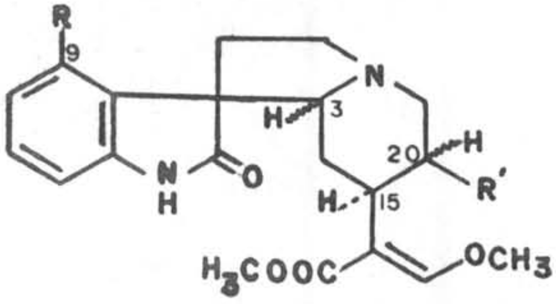
** = semi-synthetic

( ) = not yet isolated from *Uncaria* species.

N.B. *pseudo* oxindoles are too unstable to exist (Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968).

Gambirdine and isogambirdine C(9)-H, are two interconvertible stereoisomers of mitraphylline. There is no definitive information concerning their stereochemistry (Saxton, 1973).

b. <u>Tetracyclic oxindoles</u>



Alkaloid	Configuration	C(7)/series	C(9)-R	C(20)-R'
isorhynchophylline*	*normal*	A	H	CH_2-CH_3
rhynchophylline*	*normal*	B	H	CH_2-CH_3
corynoxine	*allo*	A	H	CH_2-CH_3
corynoxine B	*allo*	B	H	CH_2-CH_3
isocorynoxeine	*normal*	A	H	$CH=CH_2$
corynoxeine	*normal*	B	H	$CH=CH_2$
rotundifoline(*)	*normal*	A	OH	CH_2-CH_3
isorotundifoline(*)	*normal*	B	OH	CH_2-CH_3
(mitrafoline)	*allo*	A	OH	CH_2-CH_3
(isomitrafoline)	*allo*	B	OH	CH_2-CH_3
(isospeciofoline)	*epiallo*	A	OH	CH_2-CH_3
speciofoline	*epiallo*	B	OH	CH_2-CH_3
(rotundifoleine)	*normal*	A	OH	$CH=CH_2$
(isorotundifoleine)	*normal*	B	OH	$CH=CH_2$
(rhynchociline)	*normal*	A	OCH_3	CH_2-CH_3
(ciliaphylline)	*normal*	B	OCH_3	CH_2-CH_3
(mitragynine oxindole A)	*allo*	A	OCH_3	CH_2-CH_3
(mitragynine oxindole B)	*allo*	B	OCH_3	CH_2-CH_3

Alkaloid	Configuration	C(7)/series	C(9)-R	C(20)-R'
(isospecionoxeine)	*normal*	A	OCH_3	$CH=CH_2$
(specionoxeine)	*normal*	B	OCH_3	$CH=CH_2$

(Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968; Phillipson and Shellard, 1968; Saxton, 1973; Phillipson and Hemingway, 1975 a; Hemingway, Houghton, Phillipson and Shellard, 1975).

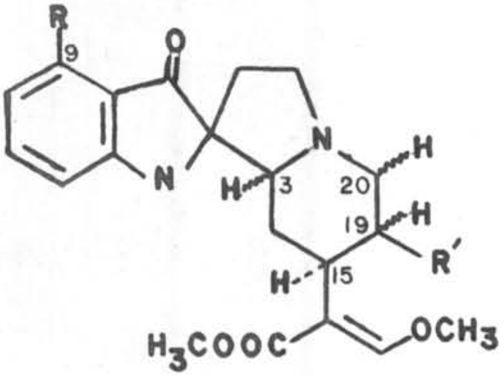
* = with its N-oxide

(*) = its N-oxide not yet isolated from *Uncaria* species

( ) = not yet isolated from *Uncaria* species.

c. Other oxindole alkaloid

Tetracyclic pseudoindoxyl



Dihydrocorynantheine pseudoindoxyl

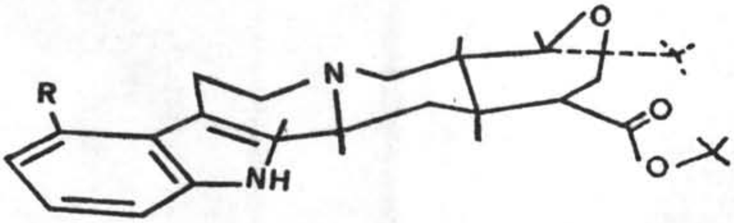
R = H, R' = CH_2-CH_3, C(3) = Hα, C(20) = Hβ, C(19) = Hβ.

5. Preferred conformations of indole alkaloids

The preferred conformations of indole alkaloids were established as follows (Trager, Lee and Beckett, 1967; Hart, Johns and Lamberton, 1967; Beecham, Hart, Johns and Lamberton, 1967; Phillipson and Shellard, 1967):-

a. Pentacyclic heteroyohimbines

NORMAL

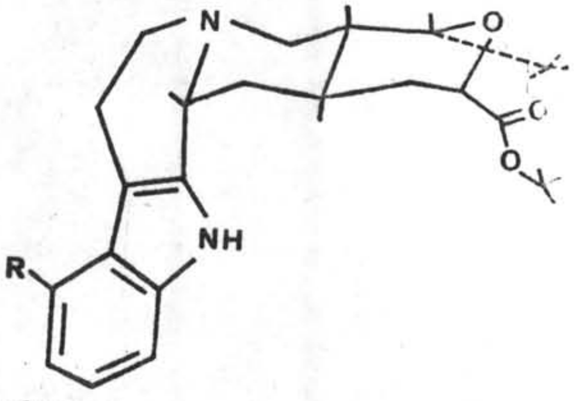


R = H, ajmalicine

R = H and C(19)CH_3-β, 19-epiajmalicine

R = OCH_3, isomitrajavine.

PSEUDO

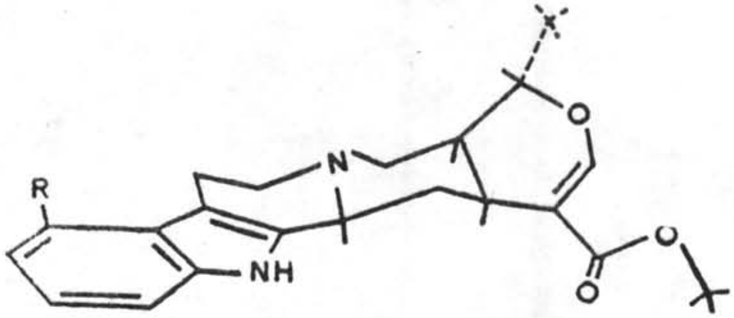


R = H, 3-isoajmalicine

R = H and C(19)CH_3-β, 19-epi-3-isoajmalicine

R = OCH_3, mitrajavine.

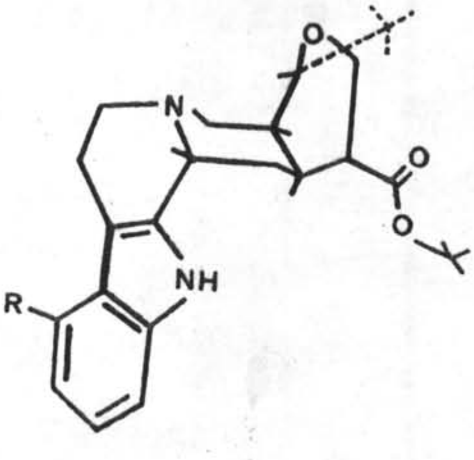
ALLO



R = H, tetrahydroalstonine

R = H and C(19)-$CH_3\beta$, rauniticine

EPIALLO



R = H, akuammigine

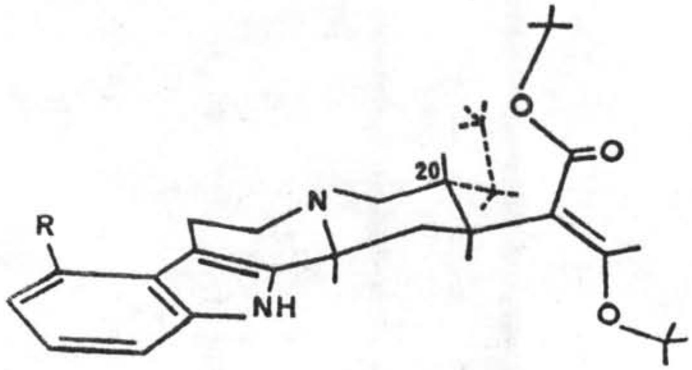
R = H and C(19)-$CH_3\beta$, 3-isorauniticine

R = H, C(14)H = OH and C(19)-$CH_3\beta$,

14-hydroxy-3-isorauniticine

b. Tetracyclic heteroyohimbines

NORMAL



R = H, dihydrocorynantheine

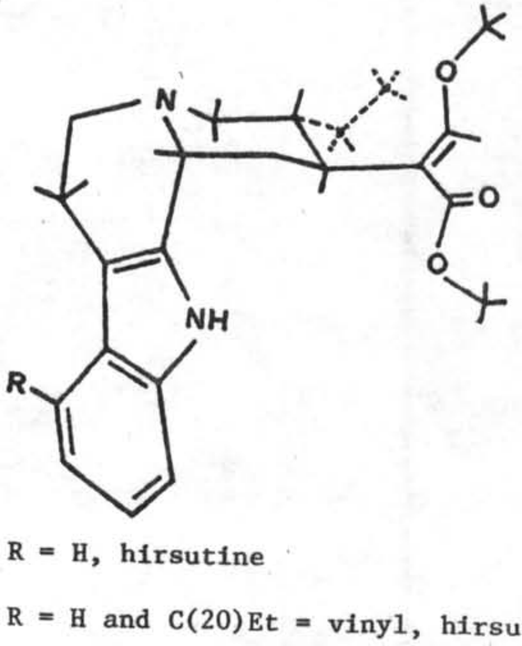
R = H and C(20)Et = vinyl, corynantheine

R = OH, gambirine

R = OCH_3, speciogynine

R = OCH_3 and C(20)Et = vinyl, paynantheine

PSEUDO



R = H, hirsutine

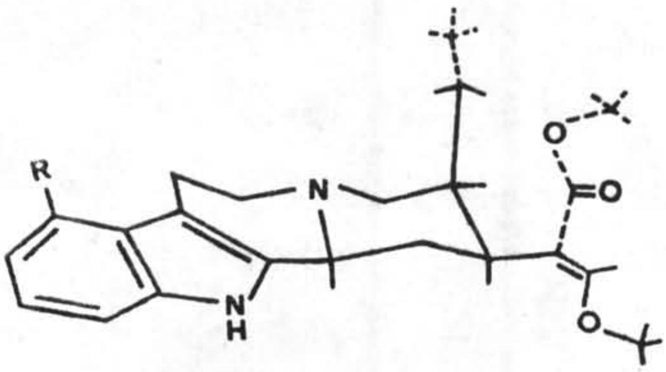
R = H and C(20)Et = vinyl, hirsuteine

R = OH, isogambirine

R = OCH_3, mitraciliatine

R = OCH_3 and C(20)Et = vinyl, isopaynantheine

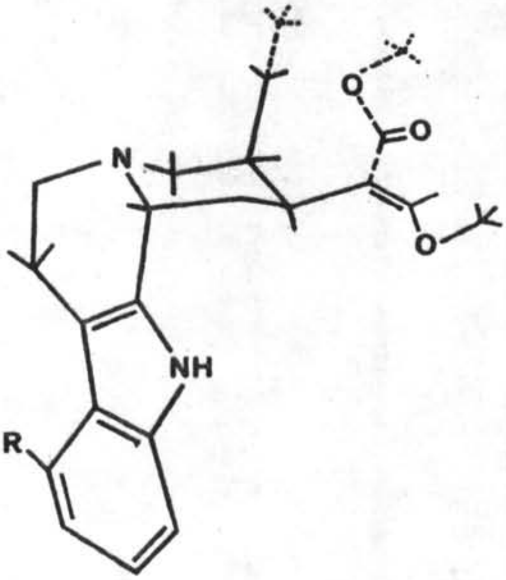
ALLO



R = H, corynantheidine

R = OCH_3, mitragynine

EPIALLO



R = H, isocorynantheidine

R = OCH_3, speciociliatine

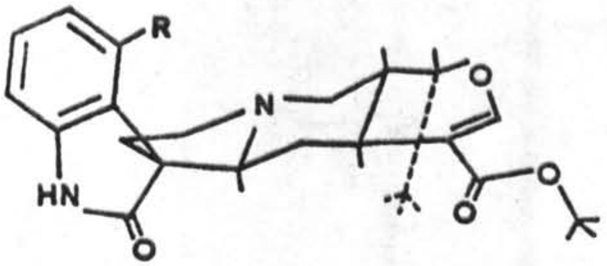
6. Preferred conformations of oxindole alkaloids

The preferred conformations of oxindole alkaloids were established as follows (Phillipson and Shellard, 1966; Trager, Lee, Phillipson and Beckett, 1967; Chan, 1969; Bindra, 1973; Saxton, 1973):-

a. Pentacyclic oxindoles

NORMAL

A.



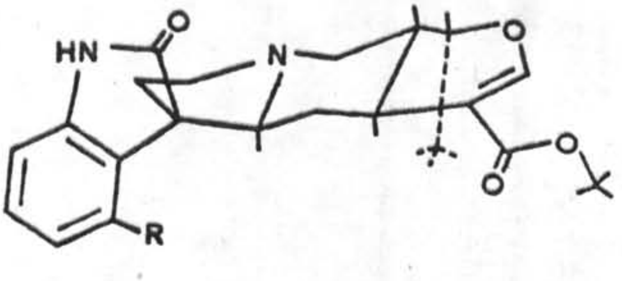
R = H, isomitraphylline

R = H and C(19)-$CH_3\beta$, uncarine A (isoformosanine)

R = OCH_3, javaphylline

NORMAL

B.



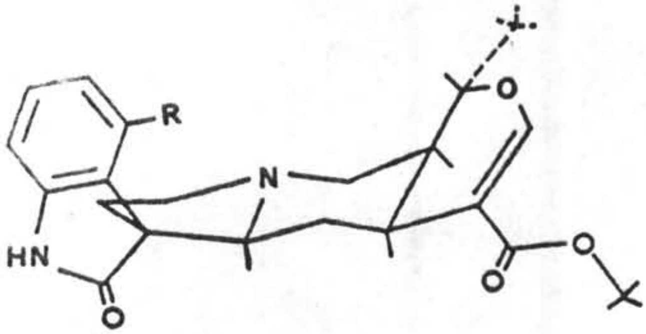
R = H, mitraphylline

R = H and C(19)-$CH_3\beta$, uncarine B (formosanine)

R = OCH_3, isojavaphylline

ALLO

A.

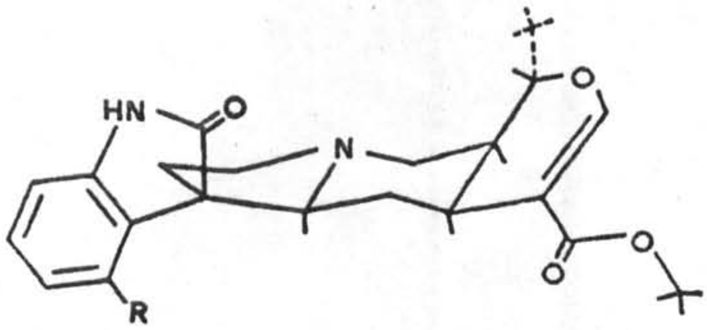


R = H, isopteropodine

R = H and C(19)-$CH_3\beta$, rauniticine oxindole A

ALLO

B.

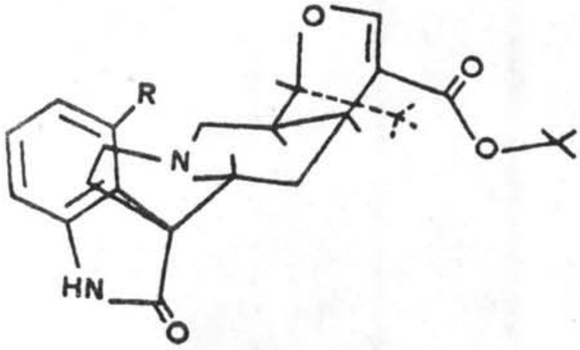


R = H, pteropodine

R = H and C(19)-$CH_3\beta$, rauniticine oxindole B

EPIALLO

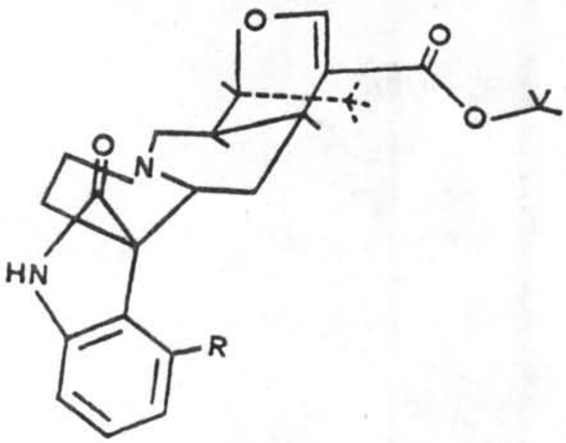
A.



R = H, speciophylline

EPIALLO

B.

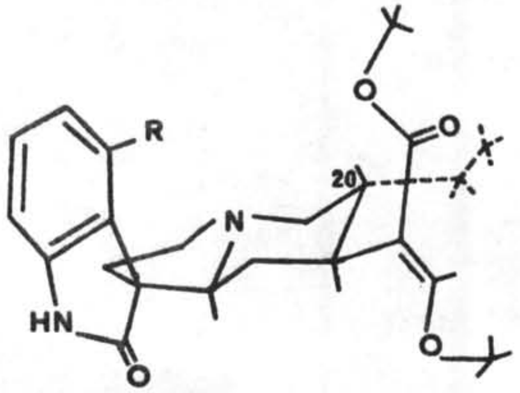


R = H, uncarine F

b. Tetracyclic oxindoles

NORMAL

A.



R = H, isorhynchophylline

R = H and C(20)Et = vinyl, isocorynoxeine

R = OH, rotundifoline

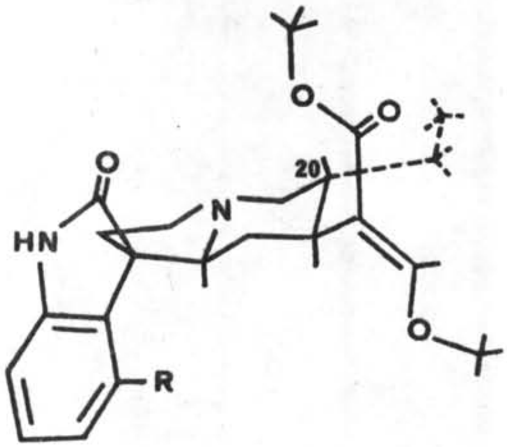
R = OH and C(20)Et = vinyl, rotundifoleine

R = OCH_3, rhynchociline

R = OCH_3 and C(20)Et = vinyl, isospecionoxeine

NORMAL

B.



R = H, rhynchophylline

R = H and C(20)Et = vinyl, corynoxeine

R = OH, isorotundifoline

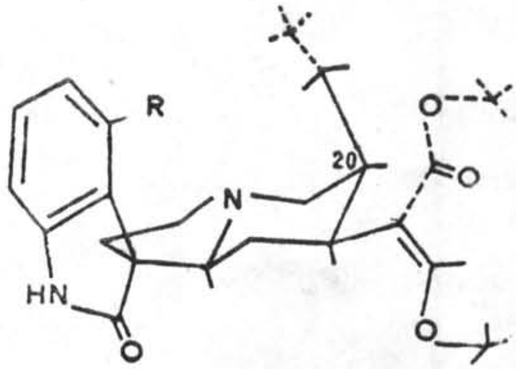
R = OH and C(20)Et = vinyl, isorotundifoline

R = OCH_3, ciliaphylline

R = OCH_3 and C(20)Et = vinyl, specionoxeine

ALLO

A.



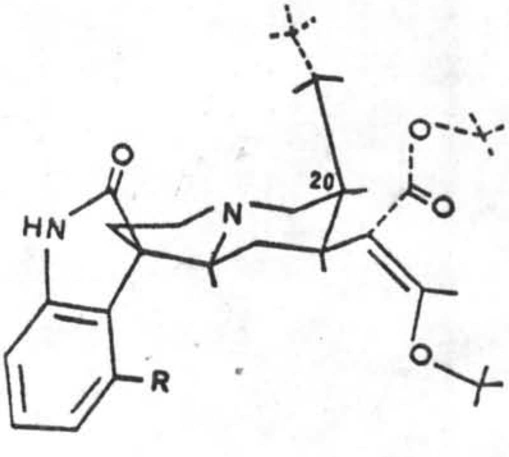
R = H, corynoxine

R = OH, mitrafoline

R = OCH_3, mitragynine oxindole A

ALLO

B.



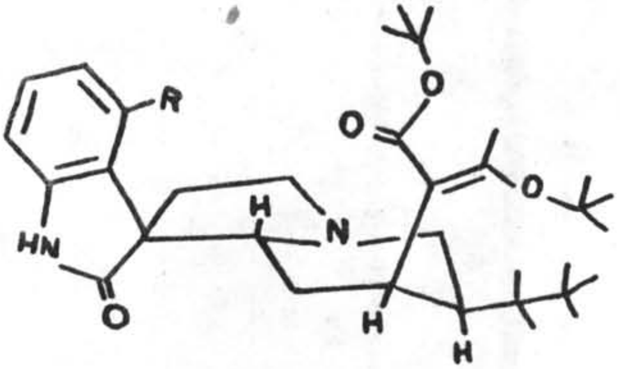
R = H, corynoxine B

R = OH, isomitrafoline

R = OCH_3, mitragynine oxindole B

EPIALLO

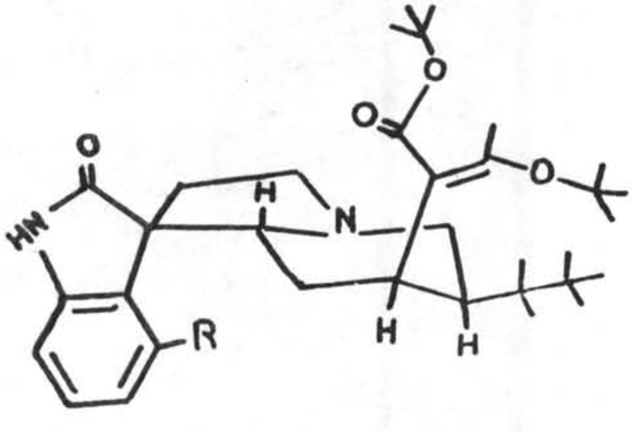
A.



R = OH, isospeciofoline

EPIALLO

B.



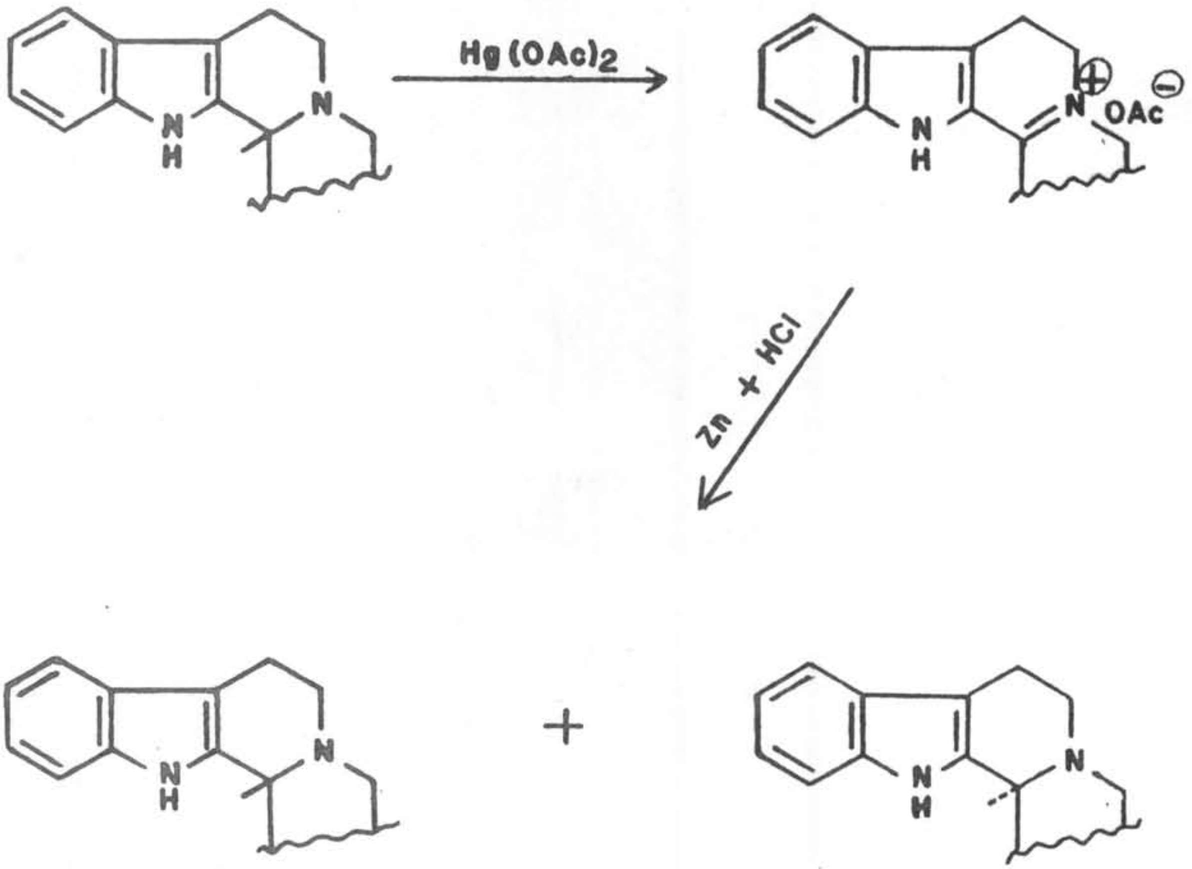
R = OH, speciofoline

7. Chemical transformations.

a. *in vitro*

1. Isomerisation of indole alkaloids

Yohimbine and heteroyohimbine alkaloids may be isomerised at C(3) by an oxidation-reduction reaction, using mercuric acetate as an oxidising agent, and zinc and hydrochloric acid as a reducing agent (Weissenborn and Diassi, 1956; Wenkert and Roychaudhuri, 1956). The reaction is shown below:-



Isomerisation of indole alkaloids

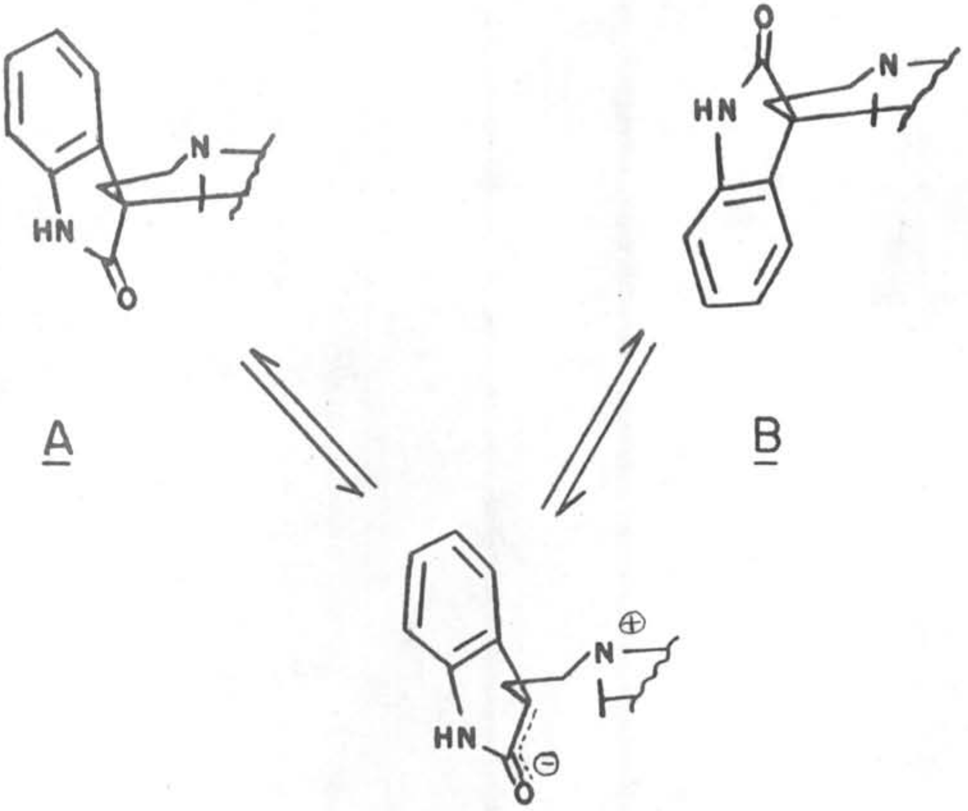
Conversion			Reference
yohimbine *(normal)*	→	pseudoyohimbine *(pseudo)*	Weissenborn and Diassi, 1956.
α-yohimbine *(allo)*	→	epi-α-yohimbine *(epiallo)*	Weissenborn and Diassi, 1956.
ajmalicine *(normal)*	→	3-isoajmalicine *(pseudo)*	Wenkert and Roychaudhuri, 1956.
tetrahydroalstonine *(allo)*	→	akuammigine *(epiallo)*	Supavita, 1979.
rauniticine *(allo)*	→	3-isorauniticine *(epiallo)*	Supavita, 1979.
mitrajavine *(pseudo)*	→	isomitrajavine *(normal)*	Shellard and Sarpong, 1971 b.
dihydrocorynantheine *(normal)*	⇌	hirsutine *(pseudo)*	Trager, Phillipson and Beckett, 1968.
corynantheidine *(allo)*	→	isocorynantheidine *(epiallo)*	Trager, Phillipson and Beckett, 1968; Shellard, Houghton and Resha, 1978 b.
speciogynine *(normal)*	→	mitraciliatine *(pseudo)*	Trager, Phillipson and Beckett, 1968.
paynantheine *(normal)*	→	isopaynantheine *(pseudo)*	Trager, Phillipson and Beckett, 1968.
mitragynine *(allo)*	→	speciociliatine *(epiallo)*	Trager, Phillipson and Beckett, 1968.

2. Isomerisation of oxindole alkaloids

In general, oxindoles may be isomerised about the C(3) and/or C(7) centres by treatment with either pyridine or acetic acid or simply by heating. The isomerisation involves scission of the C(3)-C(7) bond and hence possible inversion of one or both of the centres. Starting with a given isomer, four isomeric compounds should result upon isomerisation i.e. two (A and B) with C(3)-Hα and two (A and B) with C(3)-Hβ. A *normal* oxindole gives only two products, *normal* A and B, since *pseudo* oxindole are unstable too exist. The relative ratios of the isomers so obtained will reflect their relative stabilities in the equilibrating system (Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968).

Equilibration studies with yohimbine oxindoles A and B showed the strong base B predominate after acid treatment while the weaker A predominate after refluxing in pyridine. The energy difference in both basis is quite small, as both oxindoles are present to a considerable extent in either equilibrium mixture (Finch and Taylor, 1962 b).

Interconversions of oxindoles A and B



The examples of the interconversion and equilibration studies are summarised below:-

Reagent	Starting isomer	Conversion product	Reference
pyridine	isomitraphylline or mitraphylline	80% isomitraphylline (A), 20% mitraphylline (B)	Seaton, Nair, Edwards and Marion, 1960.
acetic acid	isomitraphylline or mitraphylline	20% isomitraphylline (A), 80% mitraphylline (B)	Beckett, Shellard, Phillipson and Lee, 1966 a.

Reagent	Starting isomer	Conversion product	Reference
pyridine	uncarine A or uncarine B	80% uncarine A (A), 20% uncarine B (B)	Seaton, Nair, Edwards, and Marion, 1960.
pyridine	isorhynchophylline or rhynchophylline	70% isorhynchophylline(A), 30% rhynchophylline (B)	Seaton, Nair, Edwards, and Marion, 1960.
pyridine	isorhynchophylline or rhynchophylline	80% isorhynchophylline(A), 20% rhynchophylline (B)	Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968.
acetic acid	isorhynchophylline or rhynchophylline	20% isorhynchophylline(A), 80% rhynchophylline (B)	Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968.
pyridine	corynoxine or corynoxine B	80% corynoxine (A), 20% corynoxine B (B)	Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968.
acetic acid	corynoxine or corynoxine B	20% corynoxine (A), 80% corynoxine B (B)	Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968.
pyridine	specionoxeine or isospecionoxeine	65% specionoxeine (A), 35% isospecionoxeine (B)	Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968.

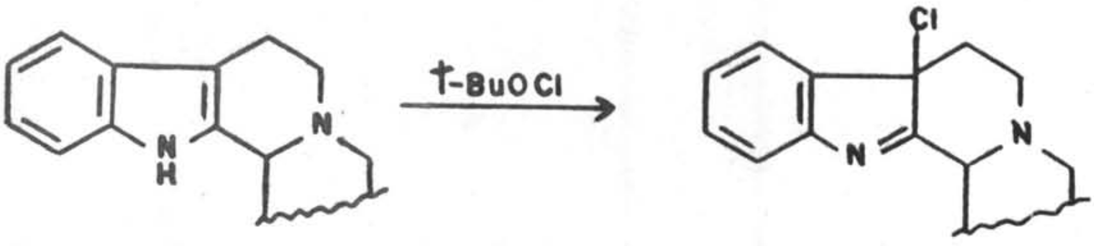
Reagent	Starting isomer	Conversion product	Reference
acetic acid	specionoxeine or isospecionoxeine	50% specionoxeine (A), 50% isospecionoxeine (B)	Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968.
pyridine	rotundifoline or isorotundifoline	90% rotundifoline (A), 10% isorotundifoline (B)	Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968.
acetic acid	rotundifoline or isorotundifoline	60% rotundifoline (A), 40% isorotundifoline (B)	Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968.
pyridine	rhynchociline or ciliaphylline	35% rhynchociline (A), 65% ciliaphylline (B)	Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968.
acetic acid	rhynchociline or ciliaphylline	50% rhynchociline (A), 50% ciliaphylline (B)	Trager, Lee, Phillipson, Haddock, Dwuma-Badu and Beckett, 1968.

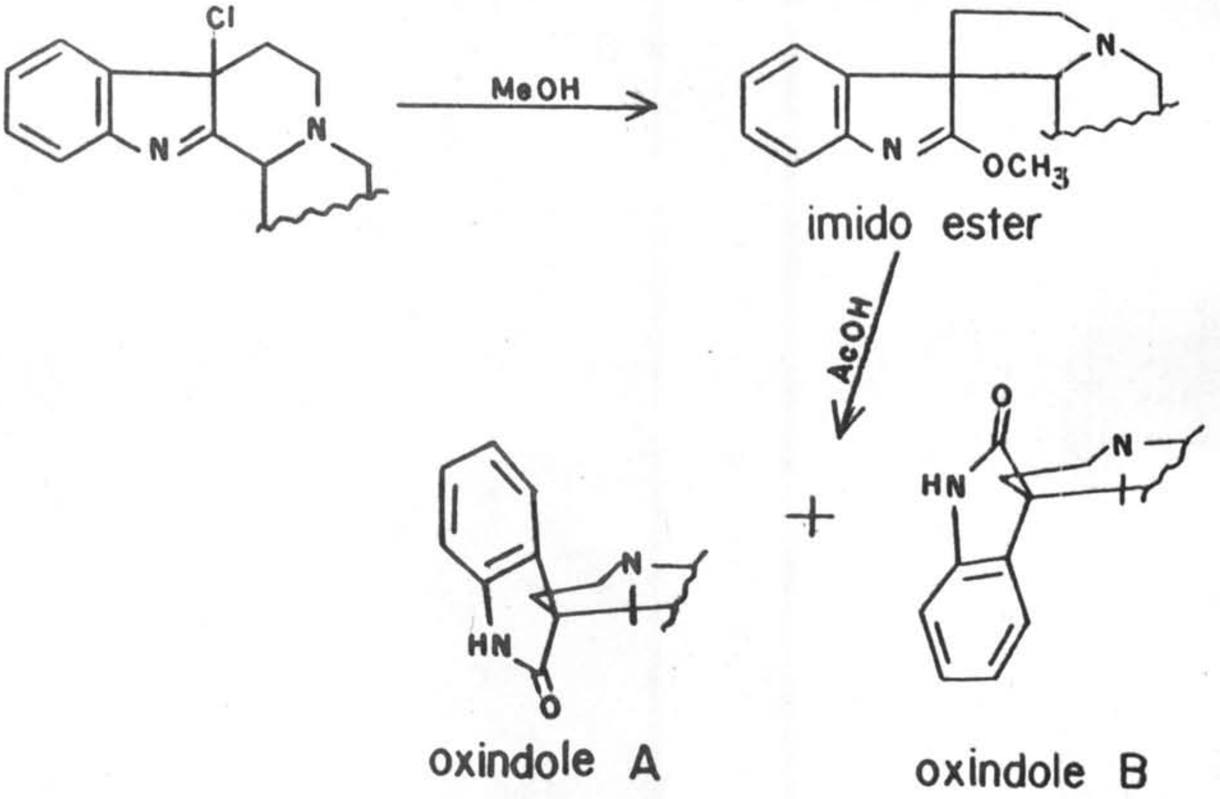
Reagent	Starting isomer	Conversion product	Reference
pyridine	mitrafoline or speciofoline	40% mitrafoline (*allo* A), 40% speciofoline (*epiallo* B), 10% isomitrafoline (*allo* B), 10% isospeciofoline (*epiallo* A)	Hemingway, Houghton, Phillipson and Shellard, 1975.
acetic acid	mitrafoline or speciofoline	50% mitrafoline (*allo* A), 25% speciofoline (*epiallo* B), 15% isomitrafoline (*allo* B), 10% isospeciofoline (*epiallo* A)	Hemingway, Houghton, Phillipson and Shellard, 1975.
pyridine	isomitrafoline or isospeciofoline	mitrafoline and speciofoline were the major products and that isomitrafoline and isospeciofoline were the minor products.	Hemingway, Houghton, Phillipson and Shellard, 1975.
pyridine	pteropodine	90% pteropodine, 10% isopteropodine	Beecham, Hart, Johns and Lamberton, 1968.
	speciophylline	20% pteropodine, 30% speciophylline, 20% isopteropodine, 30% uncarine F	
	isopteropodine	traces of pteropodine, 100% isopteropodine	

Reagent	Starting isomer	Conversion product	Reference
pyridine	uncarine F	20% pteropodine, 10-20% speciophylline, 20% isopteropodine, 40-50% uncarine F	Beecham, Hart, Johns and Lamberton, 1968.
acetic acid	pteropodine or isopteropodine or speciophylline or uncarine F	40% pteropodine, 40% speciophylline, 10% isopteropodine, 10% uncarine F	Beecham, Hart, Johns and Lamberton, 1968.

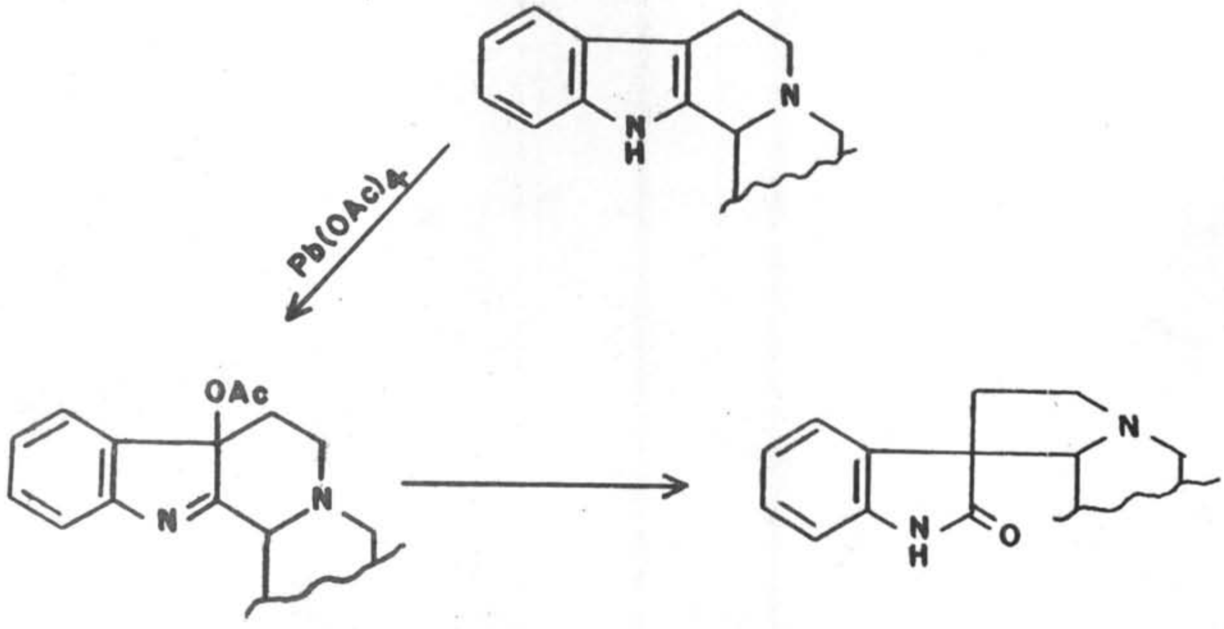
3. Conversion of indoles to oxindoles

Yohimbine and heteroyohimbine alkaloids are transformed into an epimeric mixture of chloroindolenines when oxidised by tertiary butyl hypochlorite. The chloroindolenines are then methanolysed to give the imido ester, which on acid hydrolysis yield a mixture of oxindoles A and B (Shavel and Zinnes, 1962; Finch and Taylor, 1962 b).





Another method of converting indoles to oxindoles is by using lead tetraacetate to give an acetoxy indolenine which on refluxing with methyl alcohol containing acetic acid gives the oxindoles (Hart, Johns and Lamberton, 1967). The reaction is shown below:-

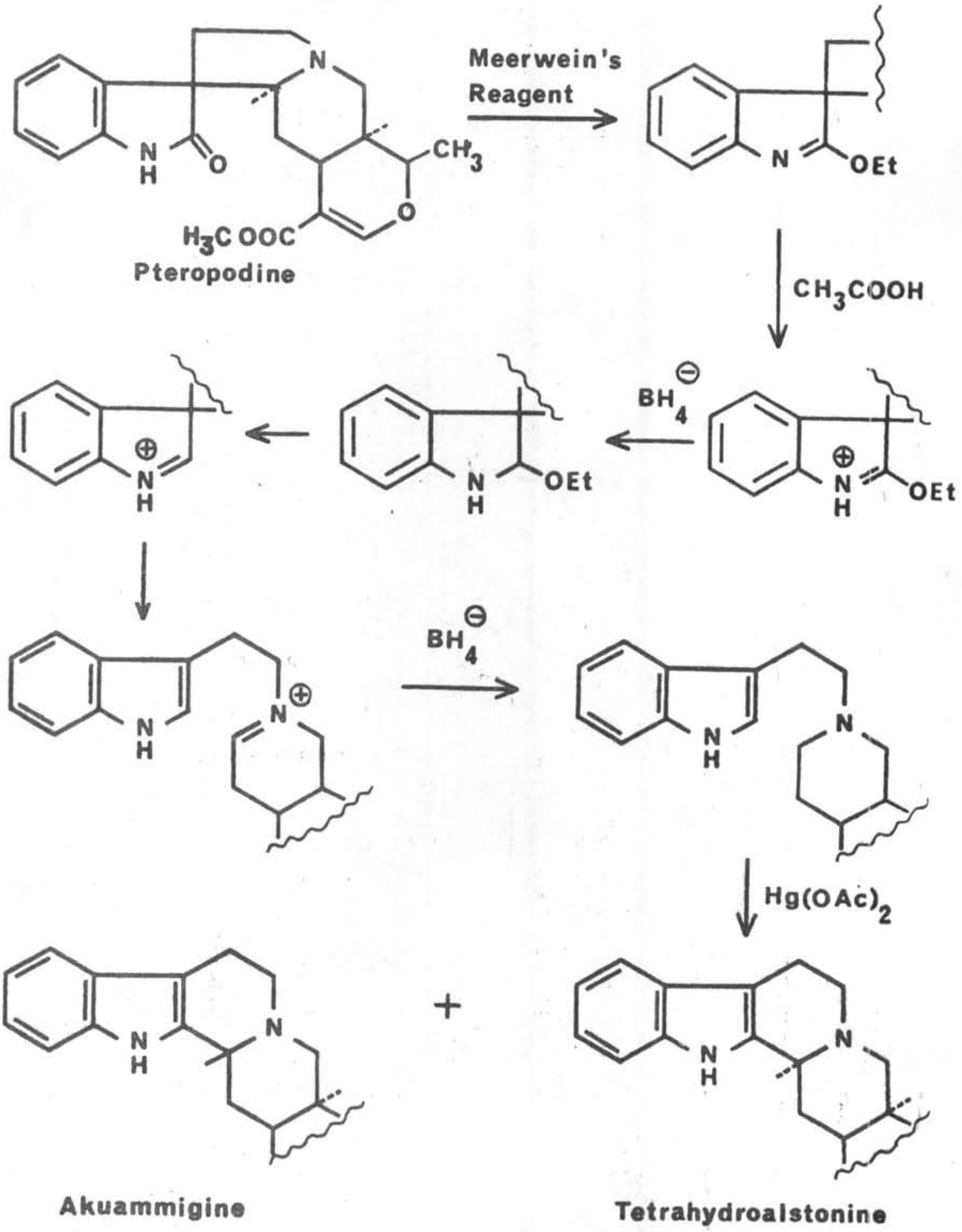


Conversion of indoles to oxindoles

Indole	Oxindole	Reference
ajmalicine (*normal*)	isomitraphylline (*normal* A) and mitraphylline (*normal* B)	Shavel and Zinnes, 1962; Finch and Taylor, 1962 b.
tetrahydroalstonine (*allo*)	isopteropodine (*allo* A), pteropodine (*allo* B), speciophylline (*epiallo* A), and uncarine F (*epiallo* B)	Hart, Johns and Lamberton, 1967.
mitrajavine (*pseudo*)	javaphylline (*normal* A) and isojavaphylline (*normal* B)	Shellard and Phillipson, 1971 a.
corynantheine (*normal*)	corynoxeine (*normal* B)	Finch and Taylor, 1962 b.
dihydrocorynantheidine (*normal*)	isorhynchophylline (*normal* A) and rhynchophylline (*normal* B)	Finch and Taylor, 1962 b.
mitraciliatine (*pseudo*)	rhynchociline (*normal* A) and ciliaphylline (*normal* B)	Shellard and Phillipson, 1971 a.

4. Conversion of oxindoles to indoles

Aimi, Yamanaka, Endo, Sakai and Haginiwa (1972) had studied the conversion of oxindoles to indoles by treating the oxindoles with Meerwein's reagent in acetic acid to form ethylimino ethers. These were oxidatively cyclised with mercuric acetate to give indoles. The oxindoles isopteropodine and pteropodine were treated and each yielded the corresponding heteroyohimbines tetrahydroalstonine and akuammigine. The reaction is shown below :-



They had also converted isorhynchophylline into hirsutine and dihydrocorynantheine using the same reaction.

b. *in vivo*

In the *in vivo* studies of the alkaloids in *Mitragyna parvifolia* (Roxb.) Korth. Shellard and Houghton (1972 a) reported that both the *normal* and *pseudo* pentacyclic heteroyohimbines, ajmalicine and 3-isoajmalicine are converted to the *normal* pentacyclic oxindoles, isomitraphylline and mitraphylline. This result showed that the conversion of heteroyohimbines to oxindole alkaloids having C(3)-Hα configuration and also the conversion of C(3)-Hβ heteroyohimbine alkaloids to C(3)-Hα oxindole alkaloids occurred *in vivo*.

When ajmalicine was fed to the growing plant no 3-isoajmalicine was produced nor was there any evidence of indolic breakdown products but when 3-isoajmalicine was fed there was evidence of an indolic transformation product which could be an intermediate in conversion of 3-isoajmalicine to the mitraphylline. Thus showing that there was no conversion between C(3)-Hα and C(3)-Hβ heteroyohimbine alkaloids.

In this plant the enzyme systems appeared to be specific for unsubstituted alkaloids in the C(9) position, since when the C(9)-OCH_3 *normal* and *pseudo* pentacyclic heteroyohimbine alkaloids, isomitrajavine and mitrajavine were fed to the plants, there was no evidence of transformation to oxindole.

The enzyme systems were further specific for the pentacyclic alkaloids as there was no corresponding oxindole detected after feeding the living plant with the tetracyclic heteroyohimbine alkaloids.

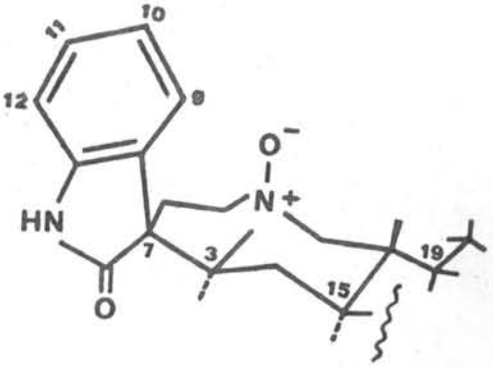
Work with ^{14}C labelled alkaloids were reported by Shellard and Houghton (1973 and 1974) and the summary of these are given in Part 3.3 "Biogenesis of *Uncaria* and *Mitragyna* alkaloids".

8. Alkaloid N-oxides

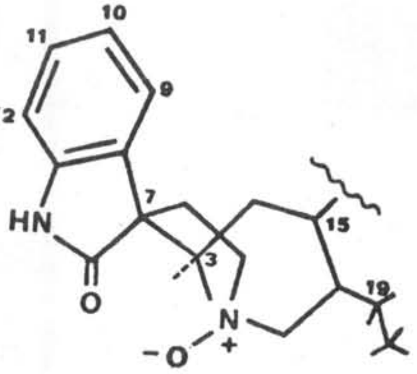
In 1964 Shellard and Phillipson reported the presence of alkaloid in the leaves of *Mitragyna rotundifolia* (Roxb.) O. Kuntze which remained on the base line of thin layer chromatograms with various solvent systems. Later, Sarpong isolated two polar alkaloids from the leaves and root of *M. inermis* (Willd.) O. Kuntze, one of which was identified to be identical with the "base-line" alkaloid previously reported and characterised to be isorhynchophylline N-oxide. The other was identified to be rhynchophylline N-oxide (Shellard, Phillipson and Sarpong, 1971).

A new polar alkaloid from the leaves of *M. tubulosa* Havil. was obtained by Rungsiyakul in 1973 and has been characterised as ciliaphylline N-oxide. In establishing the identity of this new naturally occurring N-oxide and to investigate N-oxide formation, the N-oxides of the corresponding unsubstituted oxindoles, isorhynchophylline and rhynchophylline were prepared. This investigation revealed that oxindole alkaloid with A configuration at C(7), i.e. isorhynchophylline formed two N-oxides designated as *anti*- and *syn*-, and that previously reported as isorhynchophylline N-oxide by Shellard, Phillipson and Sarpong was the *anti*-isomer. Oxindole alkaloid with B configuration formed only one

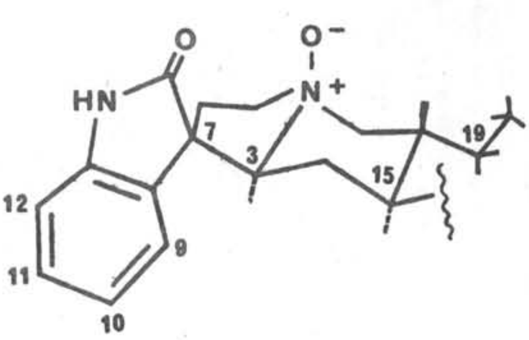
N-oxide. The absolute configurations of the four N-oxides were established as illustrated below (Phillipson, Rungsiyakul and Shellard, 1973):-



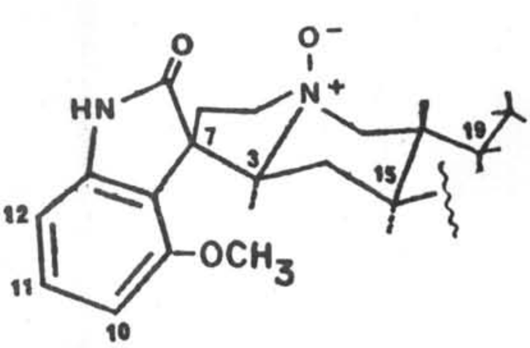
anti-isorhynchophylline N-oxide



syn-isorhynchophylline N-oxide



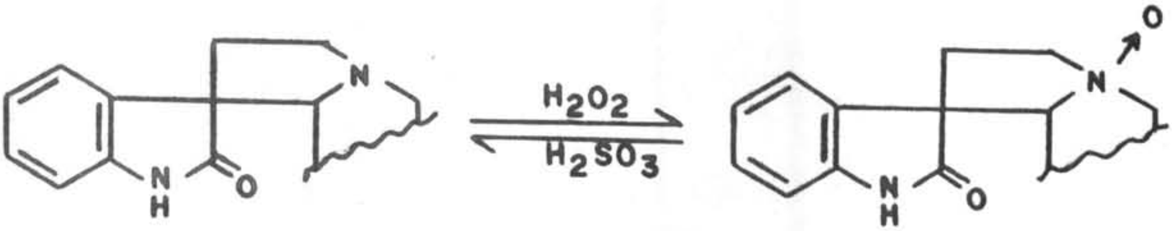
rhynchophylline N-oxide



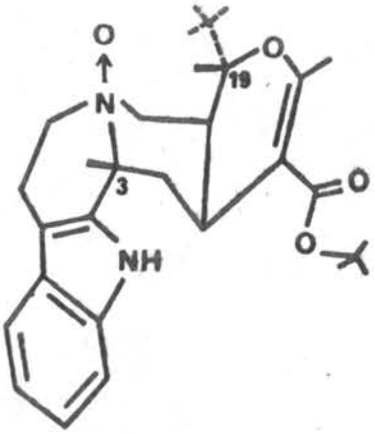
ciliaphylline N-oxide

There were two methods used in preparing alkaloid N-oxides. One was to treat the ethanolic solution of alkaloid with hydrogen peroxide overnight, followed by heating on a boiling water bath for 30 minutes and further with platinum wire for 5 minutes (Shellard, Phillipson and Sarpong, 1971; Phillipson, Rungsiyakul and Shellard, 1973). The other was to use equimolar proportions of alkaloid and *m*-chloroperbenzoic acid which were dissolved separately in chloroform and cooled to 0°-5°C. The two solutions were gradually mixed and stirred for 3 hours (Phillipson, Rungsiyakul and Shellard, 1973).

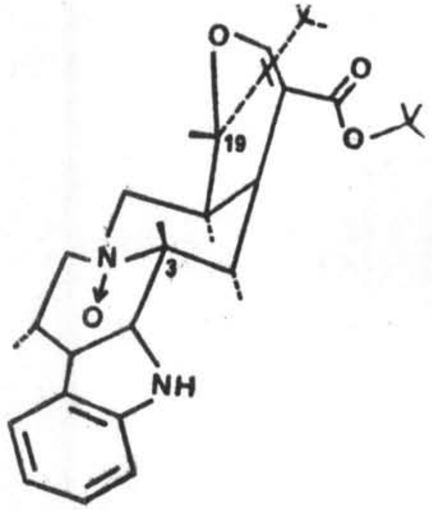
The N-oxides were readily reconverted to the parent alkaloids by the reduction with sulphurous acid overnight (Shellard, Phillipson and Sarpong, 1971; Phillipson, Rungsiyakul and Shellard, 1973).



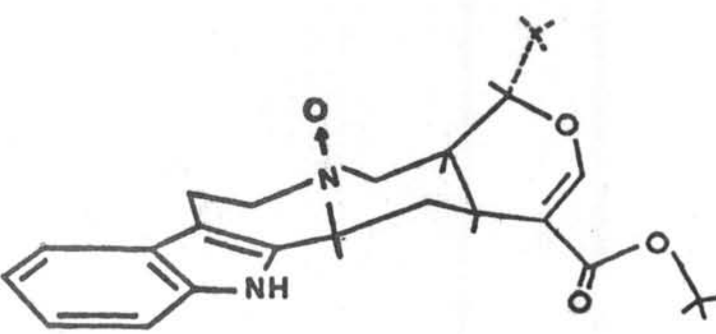
N-oxides of pentacyclic heteroyohimbines had been reported to be present in *Uncaria* species from Botanical Gardens of Singapore. They had been identified as 4 - R-akuammigine, 4 - S-akuammigine and 4 - R-tetrahydroalstonine N-oxides (Merlini, Nasini and Phillipson, 1972).



4- R-akuammigine N-oxide



4- S-akuammigine N-oxide



4- R-tetrahydroalstonine N-oxide

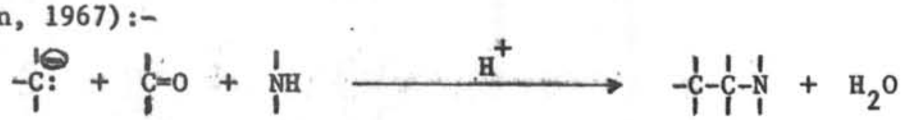
Later, N-oxides of many alkaloids have been reported to be present naturally and characterised, in particular from species of *Mitragyna* (Shellard and Rungsiyakul, 1973; Shellard and Houghton, 1973; Phillipson, Rungsiyakul and Shellard, 1973; Shellard, Houghton and Lala, 1977; Shellard and Lala, 1978) and of *Uncaria* (Phillipson and Hemingway, 1973 b and c; Hemingway and Phillipson, 1974; Phillipson and Hemingway, 1975 a; Phillipson, Hemingway and Ridsdale, 1978).

In the genus *Uncaria*, twelve N-oxides were reported to be present. They are of heteroyohimbines and oxindoles and of both pentacyclic and tetracyclic types. Their names and occurrence are given in full details in Chapter II 2. "Alkaloids isolated from species of *Uncaria*" page 11.

Biogenesis

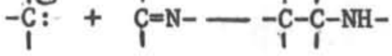
As will have been gathered from the previous chapter, plants build up a number of different alkaloid structures. In the present century much speculation has been done on how plants produce alkaloids, Robinson was a pioneer and has put forward many important ideas on alkaloid biogenesis. These speculations were based largely upon structural similarities within the alkaloid series and also upon the relations of alkaloids to simpler natural products.

One of the concepts proposed by Robinson concerning the biogenesis of alkaloids was that a wide variety of structures could be accounted for if a reaction (now know as the Mannich reaction) could occur in plants thus (Swan, 1967):-



$$-\overset{|}{\underset{|}{C}}{:}^{\ominus} + \overset{|}{\underset{|}{C}}{=}O + \overset{|}{\underset{|}{N}}H \xrightarrow{H^+} -\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{N}} + H_2O$$

The carbanion could be derived from an "activated" carbon atom or formally by the indicated shifts. The carbonyl compound and the secondary amine may be replaced by a (usually cyclic) Schiff's base (Swan, 1967):-



$$-\overset{|\ominus}{\underset{|}{C}}: + \overset{|}{\underset{|}{C}}{=}N- \longrightarrow -\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-NH-$$

1. Indole alkaloids

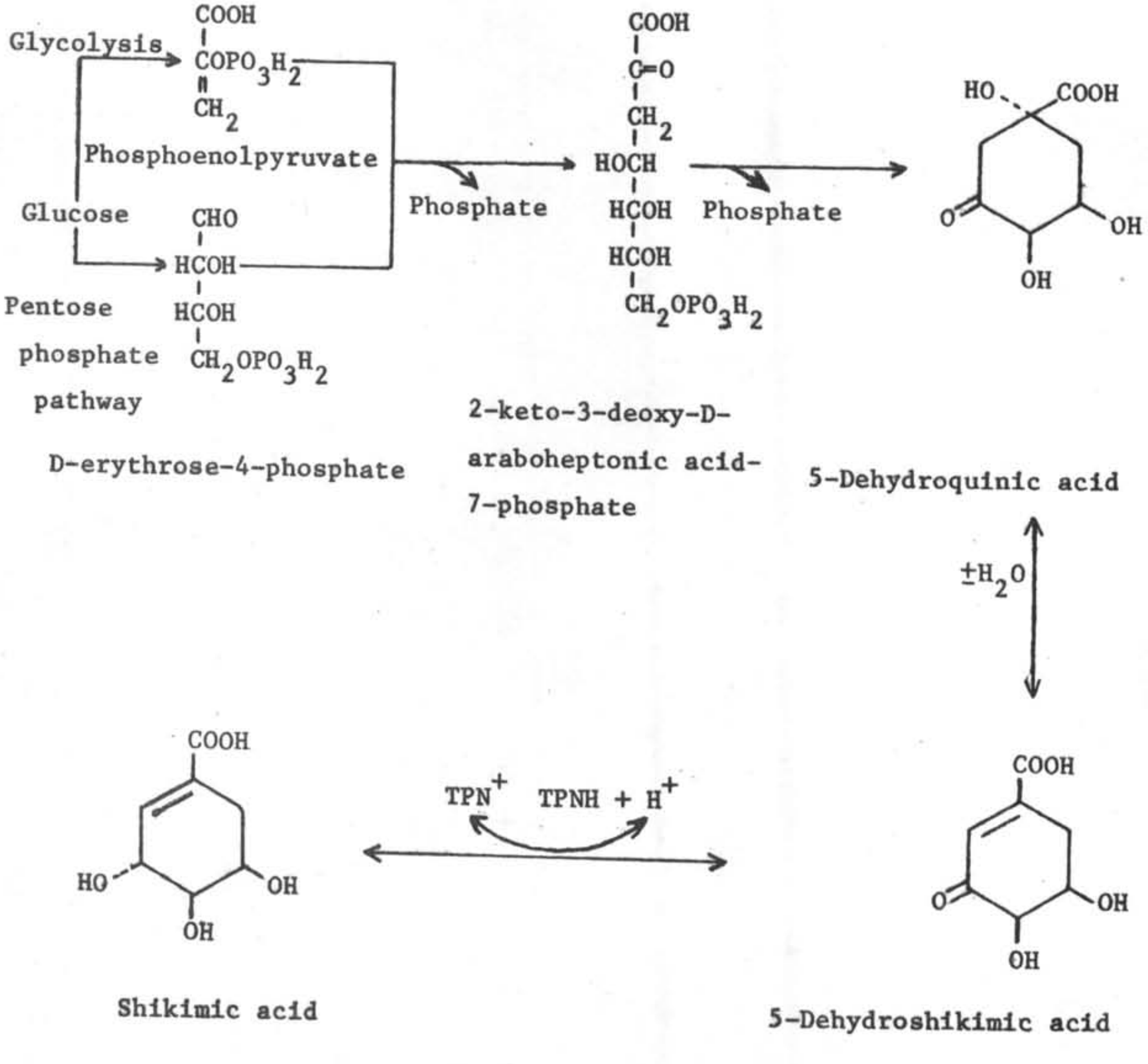
The biogenesis of indole alkaloids has excited the interest of organic chemists for many years and early speculations were reviewed by Robinson in 1955. Since then radioactive tracer studies have shown that tryptophan is the precursor of the indole portion of the majority of indole alkaloids. Tryptophan itself is derived from shikimic acid. Recently interest has been centred on the origin of the alicyclic C_{10}-moiety in the three main classes (i.e. the yohimbine, aspidosperma and iboga types), and this has culminated in the discovery that they are derived from mevalonate (Jackson and Smith, 1968). Loganin, secologanin and vincoside are also fulfil the conditions for being true precursors of the various classes of indole alkaloids (Kompis, Hesse and Schmid, 1971).

a. Formation of shikimic acid and tryptamine

1. Formation of shikimic acid

Figure below summarises the present knowledge of the pathways leading from glucose to shikimic acid. The building block for the aromatic ring are phosphoenolpyruvate and erythrose-4-phosphate, which are formed from glucose through the glycolytic and pentose phosphate pathways respectively. The condition of these two compounds to form 2-keto-3-deoxy-D-araboheptonic acid-7-phosphate (KDHP) is catalysed by an enzyme, KDHP synthetase. The cyclisation of KDHP is formed to be 5-dehydroquinic acid, and 5-dehydroshikimic acid. Shikimic acid is formed by action of a TPN-specific 5-dehydroshikimic reductase which has been found in various microorganisms and plants (Mattoon, 1963).

Formation of shikimic acid

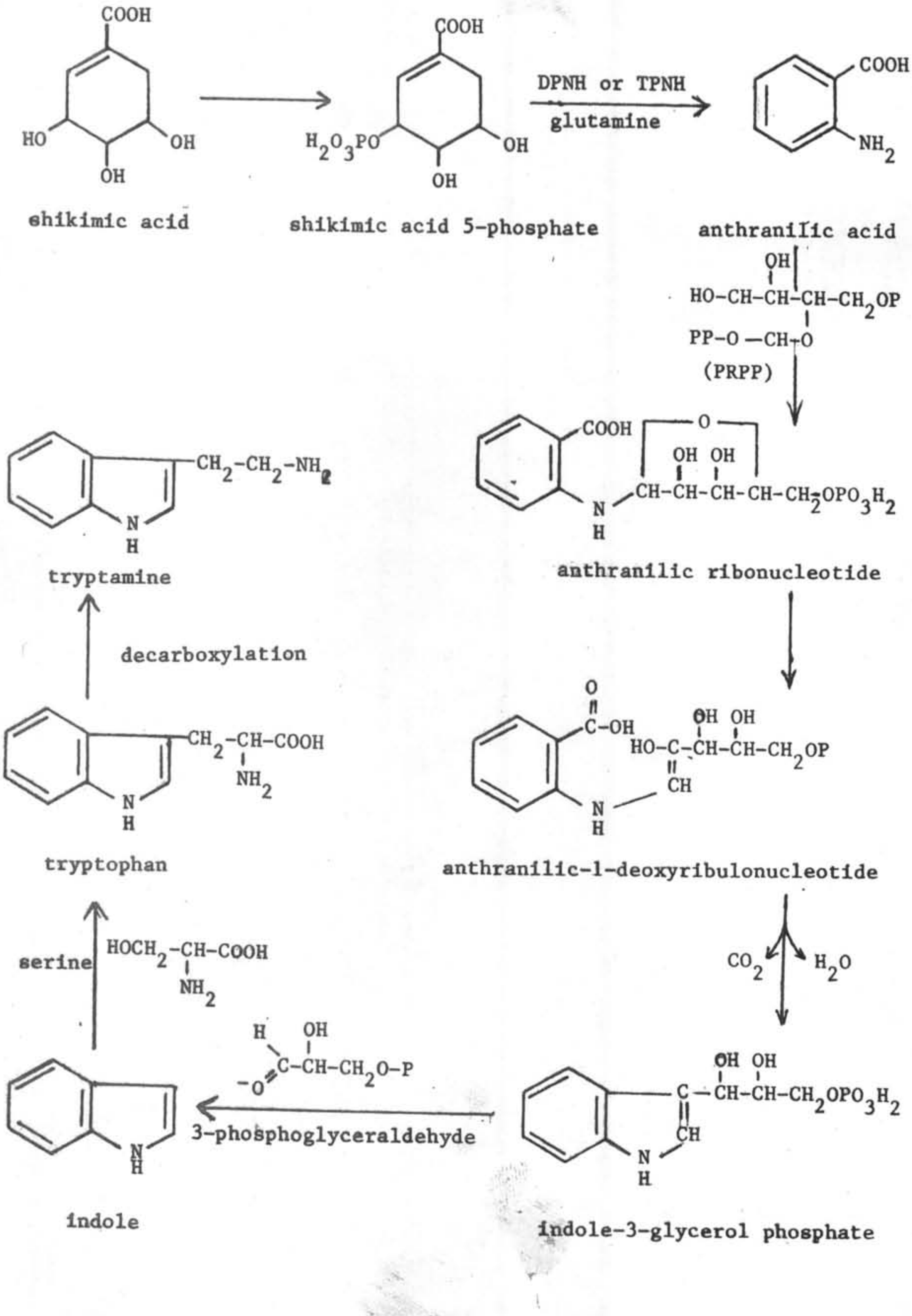


2. Formation of tryptamine

Robinson had originally suggested that the two nitrogens and the aromatic portion of all of the then-known indole alkaloids originate from tryptophan via its decarboxylation product, tryptamine. This was later experimentally proved (Kompis, Hesse and Schmid, 1971).

The amino acid tryptophan is derived from shikimic acid. By mean of a kinase reaction, shikimic acid is formed to be shikimic acid 5-phosphate. A reduction involving DPNH or TPNH and a transfer of an amino group from glutamine to the ring are involved in the formation of anthranilic acid. In the next phase of the sequence, the formation of the pyrrole ring, phosphoribosyl pyrophosphate (PRPP) provided the two necessary carbon atoms while the carbonyl carbon of anthranilic acid is lost. The immediate product of the interaction of PRPP and anthranilate is anthranilic ribonucleotide, which appears to form anthranilic 1-deoxyribulonucleotide. Ring closure, with accompanying production of CO_2 and H_2O gives rise to indole-3-glycerol phosphate. Many enzymes catalyse the reversible formation of free indole and triose phosphate or condensation of serine and indole to form tryptophan (Kompis, Hesse and Schmid, 1971; Lucker, 1972). The reaction is illustrated below:-

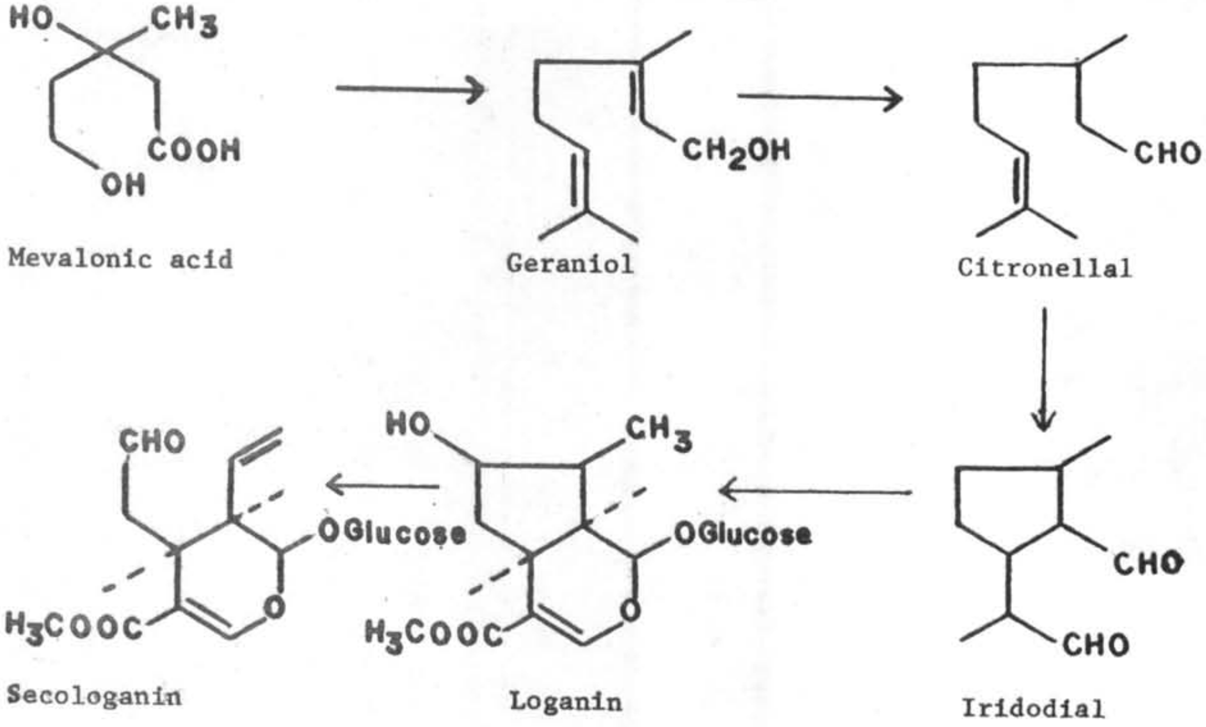
Formation of tryptamine



b. Formation of loganin and secologanin

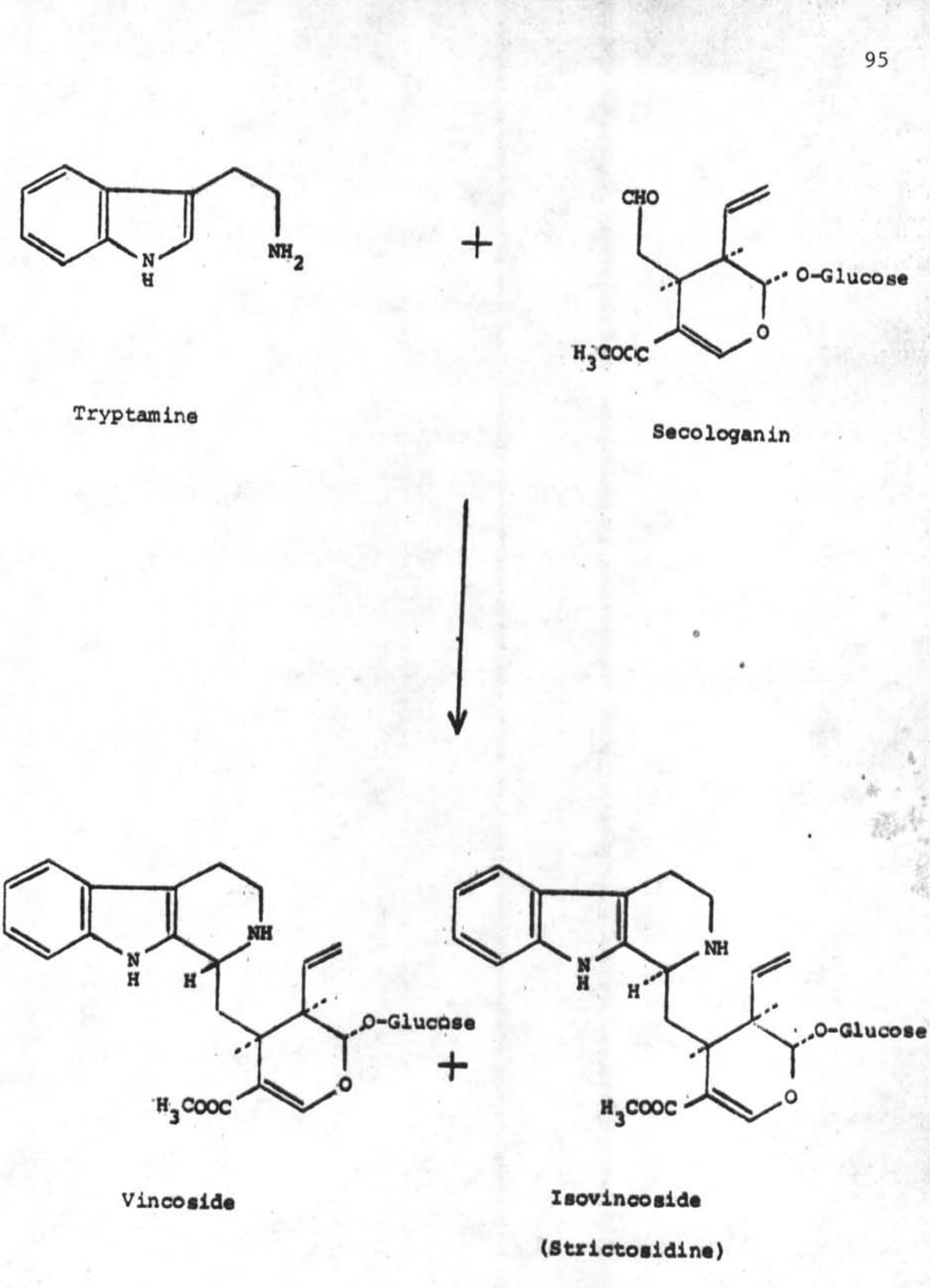
Thomas, and Battersby and his coworkers purposed a pathway of *seco*-loganin from mevalonic acid, having geraniol, citronellal, iridodial and loganin as intermediates (Battersby, Burnett and Parsons, 1968; Shellard, Phillipson and Gupta, 1969 b; Kompis, Hesse and Schmid, 1971).

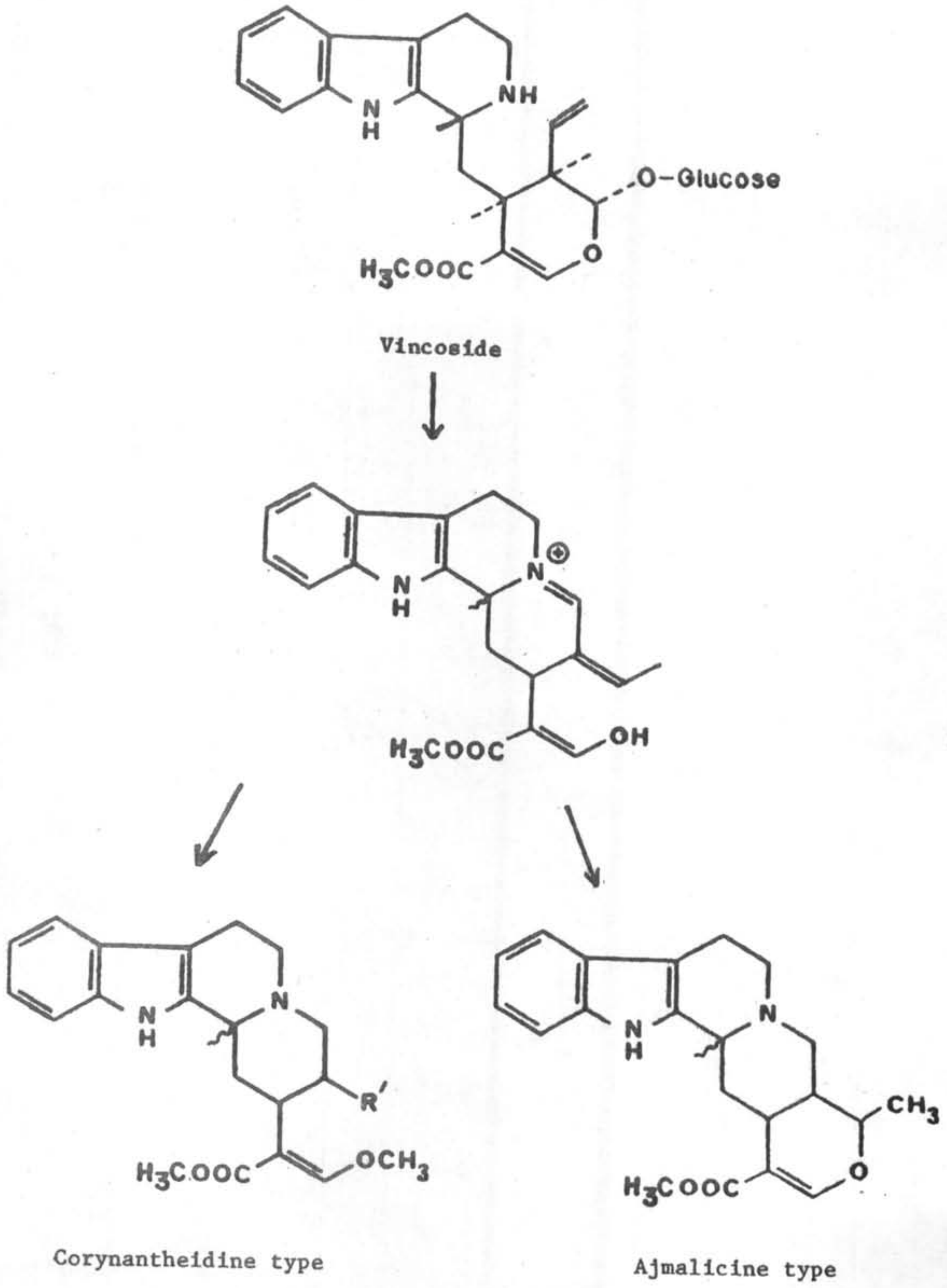
Formation of secologanin



c. Formation of pentacyclic and tetracyclic heteroyohimbines

The condensation of tryptamine and secologanin gives two diastereoisomers, vincoside (C3-Hβ) and isovincoside (C3-Hα) (Blackstock, Brown and Lee, 1971; Rueffer, Nagakura and Zenk, 1978). The biogenetic pathway to pentacyclic and tetracyclic heteroyohimbines can therefore be presented as shown in figure below (Shellard, Phillipson and Gupta, 1969 b; Rungsiyakul, 1973):-

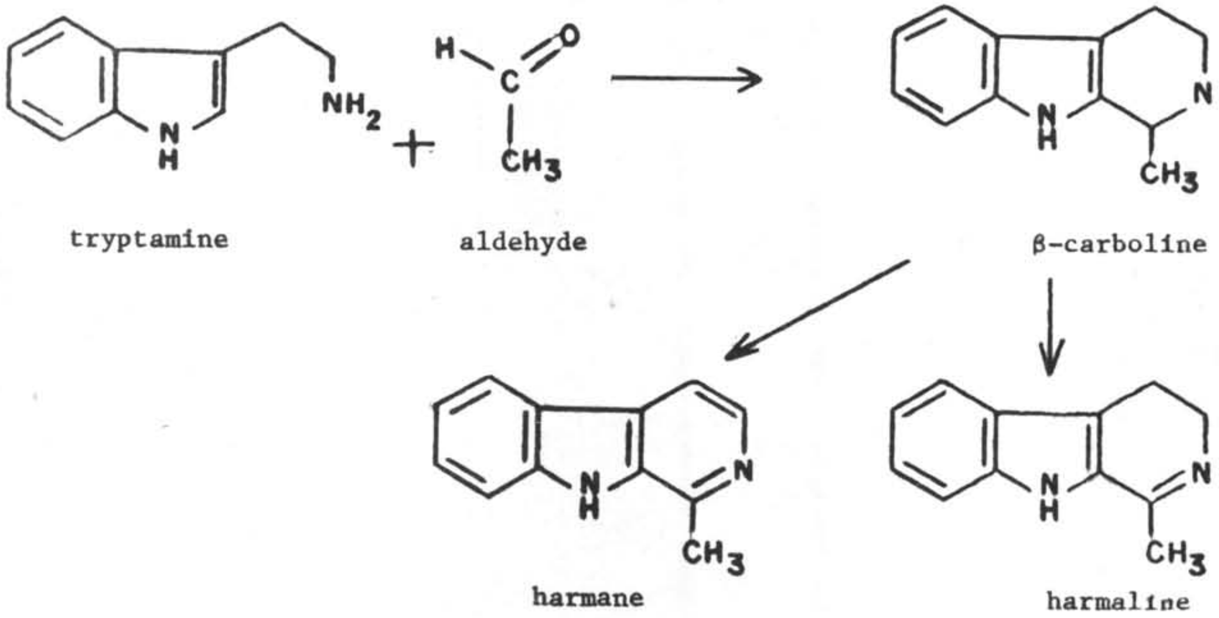

NH$_2$
N H
CHO
O-Glucose
O
H$_3$COOC
Tryptamine
Secologanin
NH
N H
H
O-Glucose
O
H$_3$COOC
Vincoside
Isovincoside
(Strictosidine)


NH
N
H
O-Glucose
O
H_3COOC
Vincoside
N⊕
N
H
OH
H_3COOC
N
N
H
R′
H_3COOC
OCH_3
Corynantheidine type
N
N
H
CH_3
O
H_3COOC
Ajmalicine type

d. Formation of other alkaloids

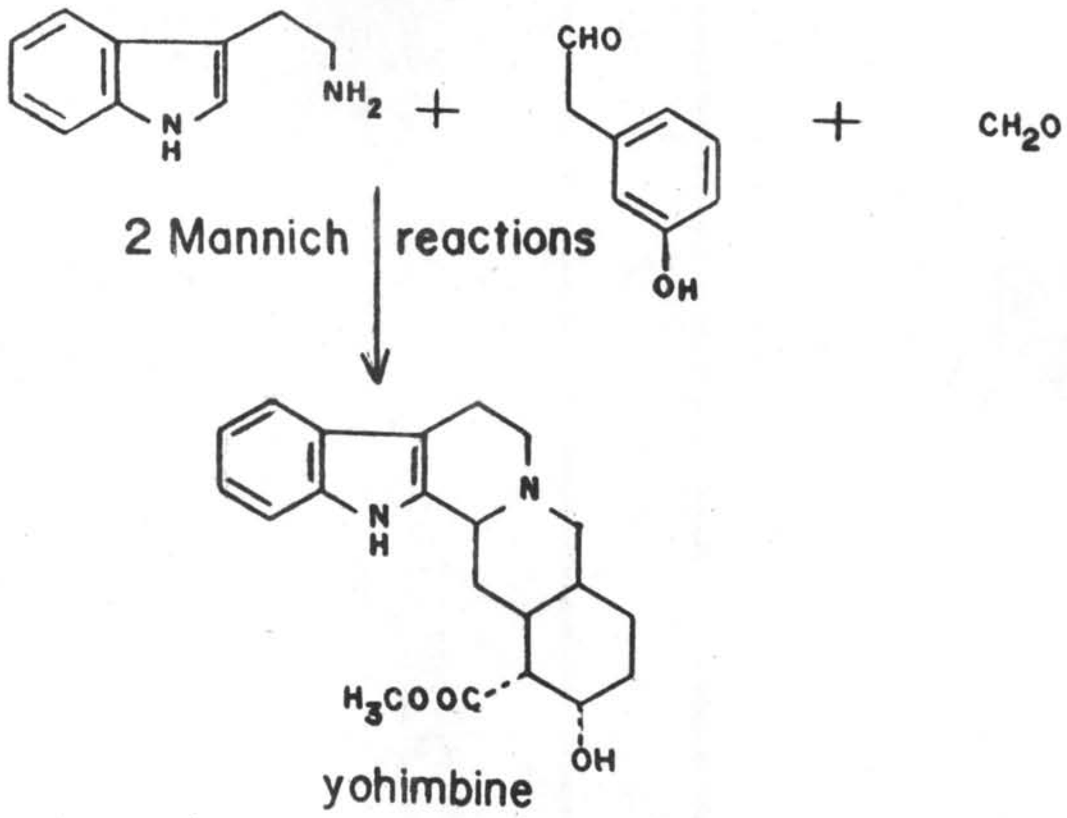
1. Formation of harmane and harmaline

The condensation between a tryptamine and aldehyde gives rise to harmane and harmaline (Robinson, 1968) as follow:-



2. Formation of yohimbine

Yohimbine was considered to be formed from tryptophan, phenylalamine or its equivalent and formaldehyde via two Mannich condensations (Taylor, 1966) as follow:-

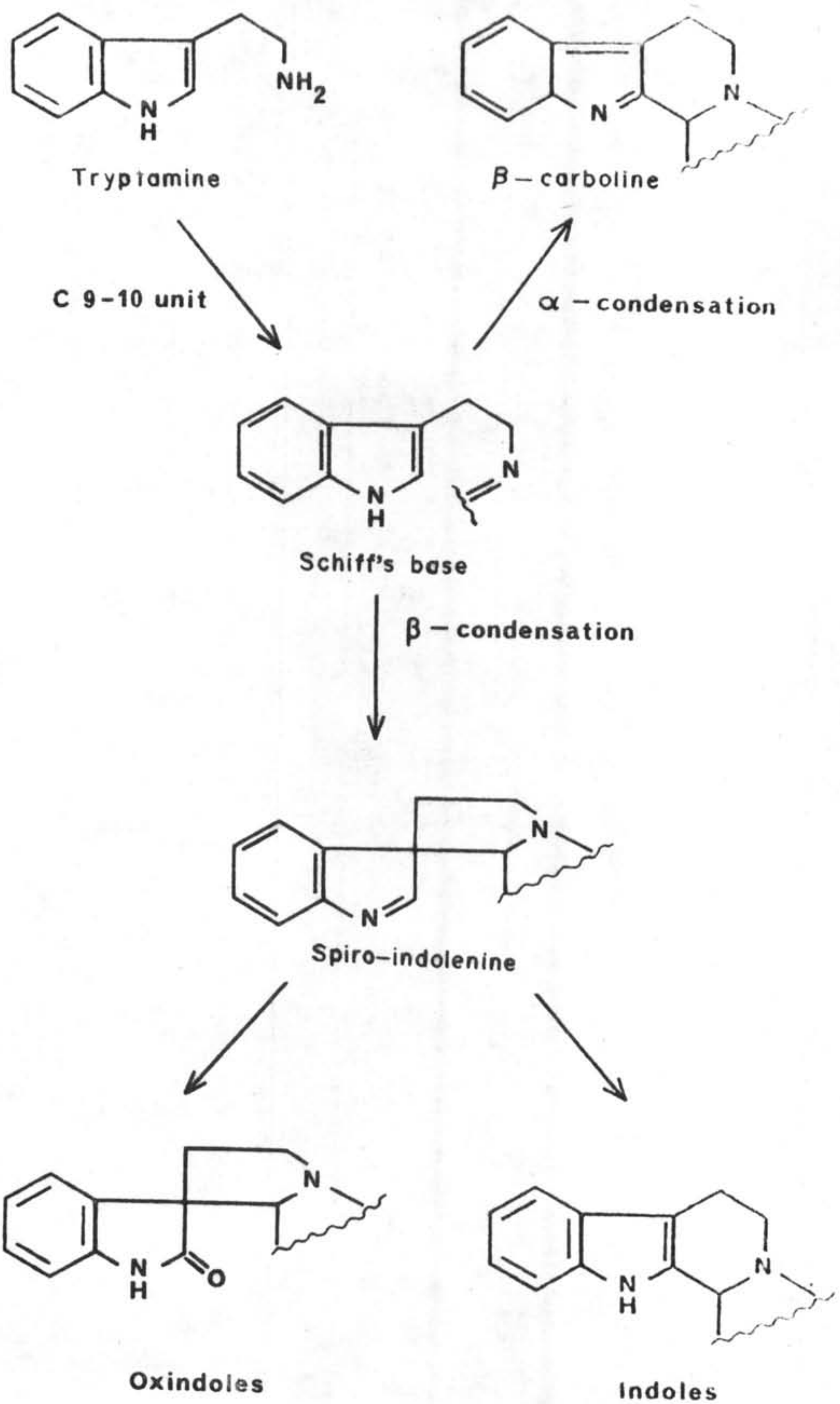


3. Formation of roxburghines and pyridino-indolo-quinolizidinones

The roxburghines are derived from a monoterpene and two tryptamine units (Phillipson, Hemingway and Ridsdale, 1978). Whereas the pyridino-indolo-quinolizidinones might arise possibly by reaction of vincoside or isovincoside-lactam with ammonia (Phillipson, Hemingway, Bisset, Houghton and Shellard, 1974).

2. Oxindole alkaloids

In 1948 Woodward suggested that the condensation of tryptamine and the C_{10} unit may be either an α condensation to give indoles or a β condensation to give oxindoles (Shellard, Phillipson and Gupta, 1969 b). Later Jackson and Smith (1968) have proposed that the initial product of the condensation of tryptamine and the alicyclic moiety (C_{9-10} unit) is presumably a Schiff's base. This base then cyclises at either the α or β position of the indole nucleus to give the β-carboline or the spiro-indolenine. They argued that the β condensation is more favoured because the resultant intermediate (spiro-indolenine) does not necessitate rearrangement of the π electron system of the benzene ring which would be the case with the α condensation. The spiro-indolenine can either isomerise in mild acid condensations to give the β-carboline and hence indole alkaloids or oxidise to give oxindole alkaloids. This can be illustrated as shown in the next page.


NH2
N
H
Tryptamine
N
N
β – carboline
C 9-10 unit
α – condensation
N
N
H
Schiff's base
β – condensation
N
N
Spiro-indolenine
N
N
H
O
Oxindoles
N
N
H
Indoles

3. The *Uncaria* and *Mitragyna* alkaloids

The majority of the *Uncaria* alkaloids reported are of the pentacyclic and tetracyclic heteroyohimbine-types and the corresponding oxindoles. The alkaloids represent variants of these structures, differing in their stereochemistry and/or aromatic substitution similar to those of the closely related genus, *Mitragyna*. The *Uncaria* and *Mitragyna* indole alkaloids are assumed to follow the pathway for indoles described above. A possible biogenetic link between the indoles and oxindoles of which are found together in *Uncaria* and *Mitragyna* species is of interest.

It was observed by Shellard, Phillipson and Gupta (1969 b) that when both indole and oxindole alkaloids occurred in *Mitragyna* species, the D/E ring systems were identical in both types of alkaloid. Furthermore, with the exception of *Mitragyna speciosa* Korth. the indole alkaloids present in the largest quantity are the thermodynamically least stable configurations i.e. *epiallo* and *Pseudo*. This gave rise to the possibility that there was a well defined biogenetic link between the formation of the indole and oxindole alkaloids and a hypothesis was put forward by Shellard, Phillipson and Gupta (1969 b), at the time when vincoside, one of the indole alkaloid precursors was believed to have C(3)-H α, that

a. the plant synthesised the thermodynamically more stable indole alkaloids according to the scheme suggested by Battersby and Hall (1969) for the biogenesis of indole alkaloids,

b. these alkaloids then isomerised into the corresponding thermodynamically less stable configuration, and

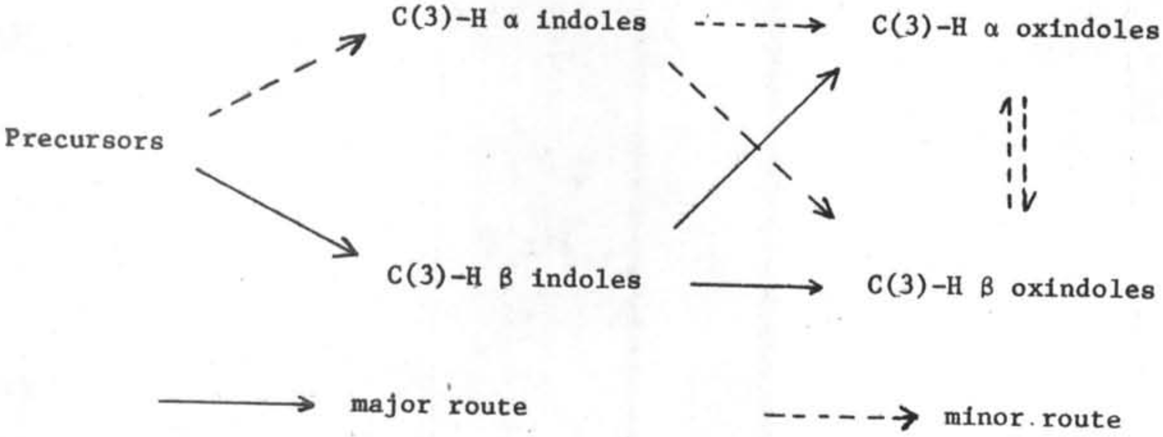
c. all the indole alkaloids were then converted to the corresponding oxindole alkaloids.

It should be noted that no *pseudo* oxindole alkaloids have been isolated and this confirms the view of Trager, Phillipson and Beckett (1968) that they are unstable to exist. These hypothesis can thus be summarised as follow:

$$\begin{tikzcd}
\begin{array}{c}\textit{normal}\text{ indoles}\\ \text{C(3)-H }\alpha\end{array} \arrow[r] \arrow[d, shift right] & \begin{array}{c}\textit{normal}\text{ oxindoles A and B}\\ \text{C(3)-H }\alpha\end{array} \\
\begin{array}{c}\textit{pseudo}\text{ indoles}\\ \text{C(3)-H }\beta\end{array} \arrow[u, shift right] &
\end{tikzcd}$$

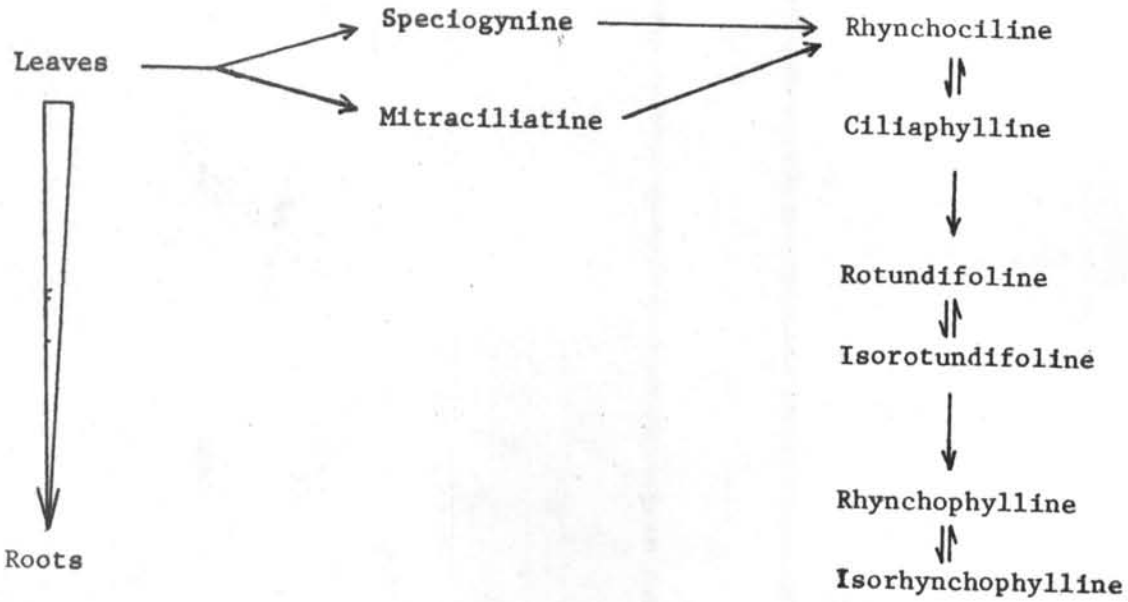
$$\begin{tikzcd}
\begin{array}{c}\textit{allo}\text{ indoles}\\ \text{C(3)-H }\alpha\end{array} \arrow[r] \arrow[d, shift right] & \begin{array}{c}\textit{allo}\text{ oxindoles A and B}\\ \text{C(3)-H }\alpha\end{array} \\
\begin{array}{c}\textit{epiallo}\text{ indoles}\\ \text{C(3)-H }\beta\end{array} \arrow[u, shift right] \arrow[r] & \begin{array}{c}\textit{epiallo}\text{ oxindoles A and B}\\ \text{C(3)-H }\beta\end{array}
\end{tikzcd}$$

However, further investigations undertaken to test the validity of the hypothesis led to major modifications. It was considered more likely that the C(3)-H α and C(3)-H β indole alkaloids were separately synthesised from a precursor but that the *pseudo* and *epiallo* indole alkaloids were the dominant ones and offered the main pathway to the oxindole alkaloids. This modification of the hypothesis later becomes more rational with Blackstock's revelation in 1971 and De Silva *et al.* in the same year (De Silva, Smith and Warren, 1971), that the C(3)-H in vincoside was actually β (isovincoside = strictosidine = α). The modifications can be indicated diagrammatically as follows (Shellard and Houghton, 1974):-

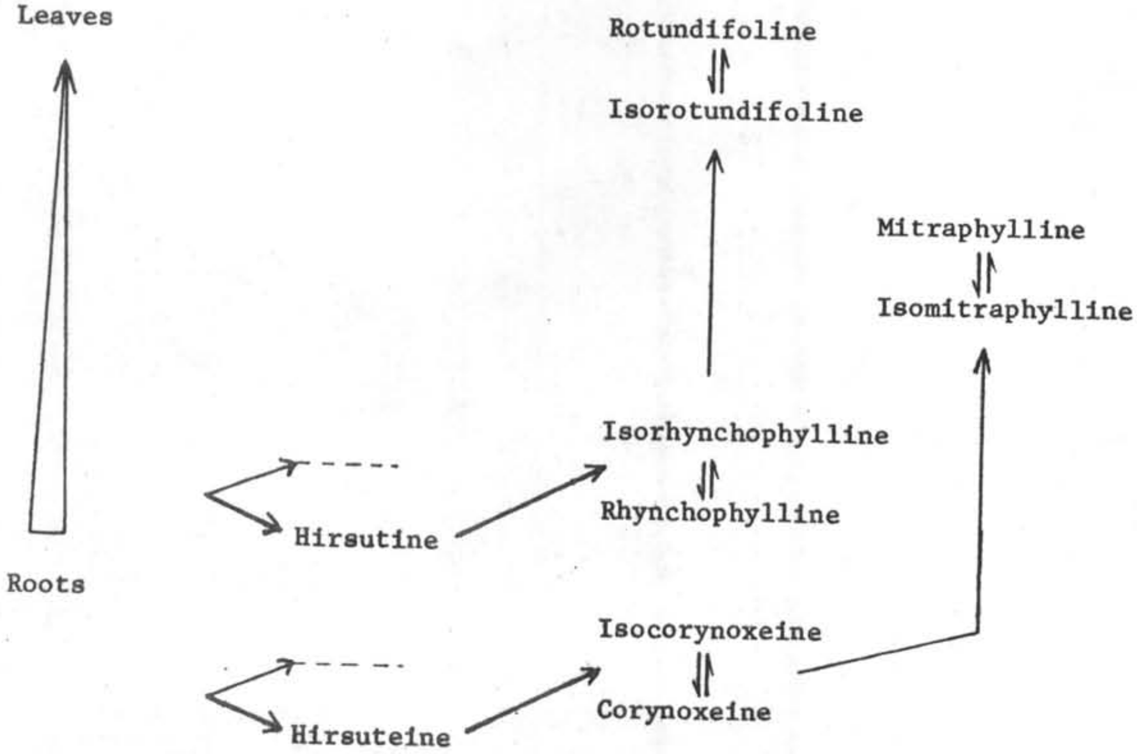


Some alkaloid patterns in *Mitragyna* species conform to the hypothesis regarding the possible biogenesis of oxindole alkaloids put forward by Shellard and Houghton (1974). The patterns and possible biogenetic sites of the alkaloids in the plant were summarised diagrammatically as follow (Shellard and Lala, 1978):-

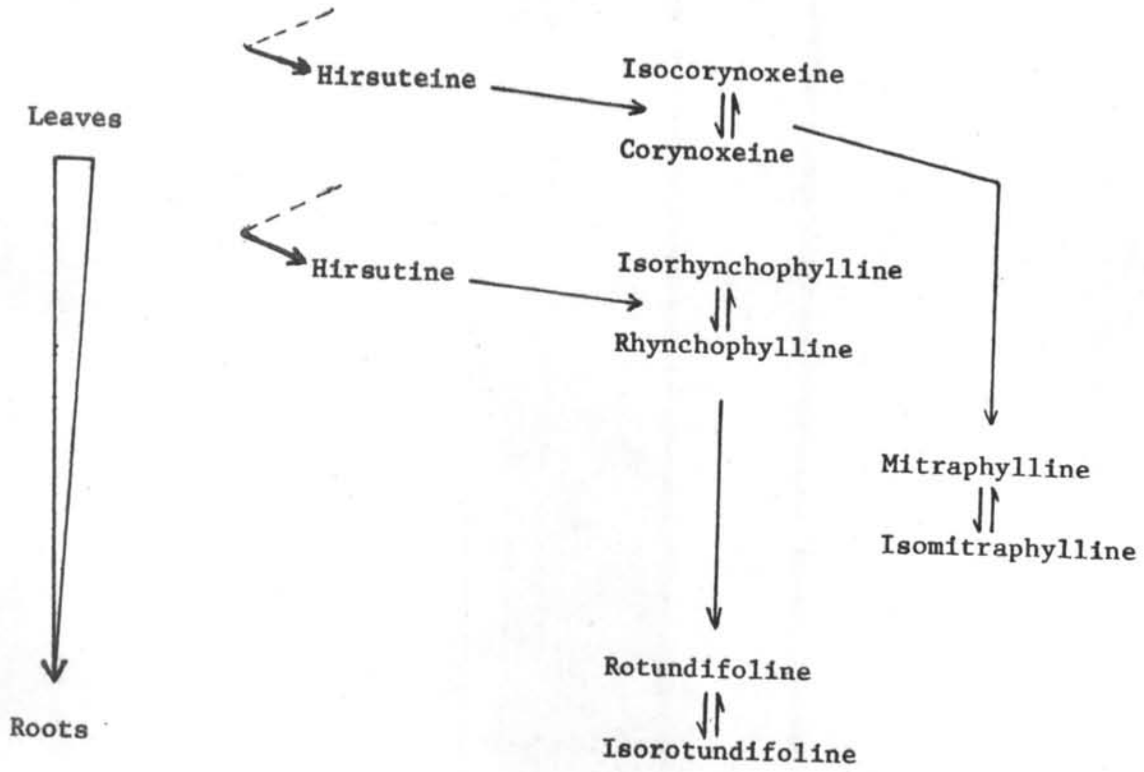
A. *Mitragyna ciliata* Aubr. et Pellegr. and *M. inermis* (Willd.) O. Kuntze



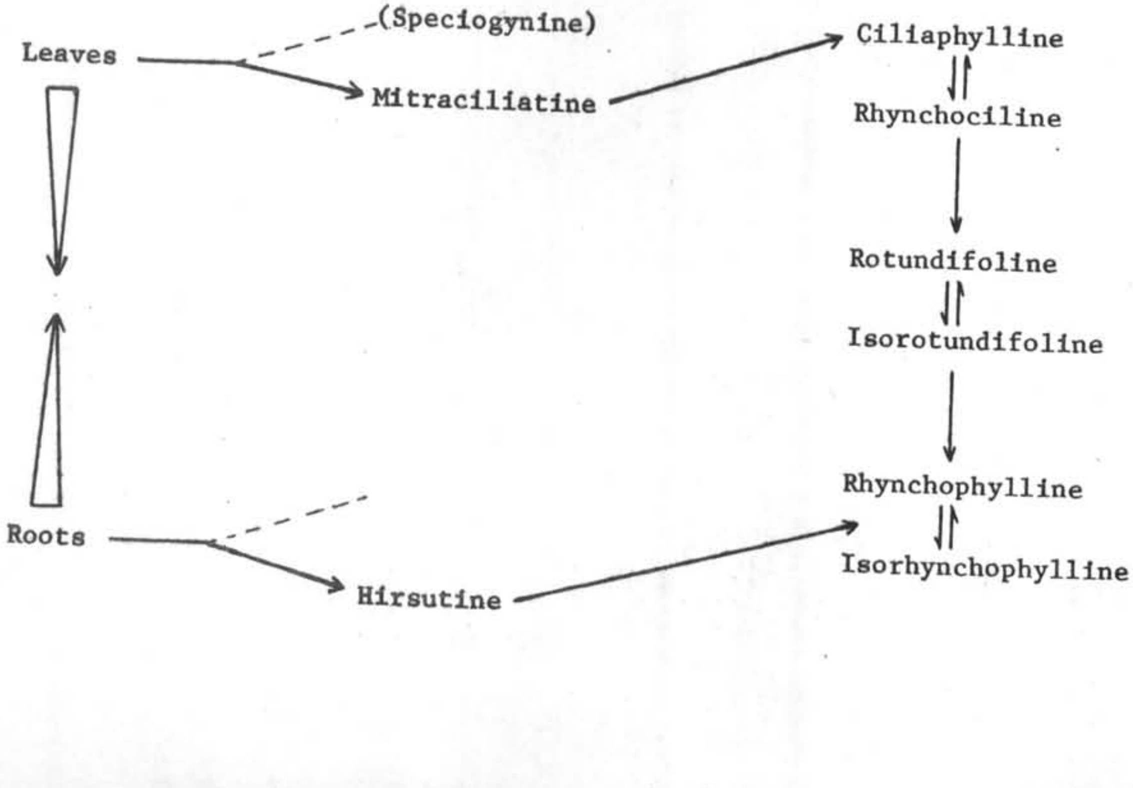
B. *M. rubrostipulata* (Schum.) Havil.



C. *Mitragyna stipulosa* (DC.) O. Kuntze



D. *M. tubulosa* Havil.



The two heteroyohimbine alkaloids tetrahydroalstonine and akuammigine found as minor alkaloids in the *Uncaria bernaysii* F.v. Muell. leaves and stems, possess D and E ring systems which are identical in structure to the major oxindole alkaloids isolated (isopteropodine, pteropodine, speciophylline and uncarine F). A similar situation exists for *U. rhynchophylla* Miq. where the tetracyclic heteroyohimbine and oxindole alkaloids isolated also have identical D/E ring systems. Since it was considered that similar relationships as postulated for *Mitragyna* species might also occurred to some extent in *Uncaria* species, the following relationships may be possible within *Uncaria bernaysii* F.v. Muell. (Phillipson and Hemingway, 1973 a):

$$\begin{tikzcd}
\begin{array}{c}\textit{allo}\text{ indole}\\ \text{(tetrahydroalstonine)}\end{array} \arrow[r, rightleftharpoons] \arrow[d, shift right] & \begin{array}{ccc}\textit{allo}\text{ oxindole A} & \text{and} & \textit{allo}\text{ oxindole B}\\ \text{(isopteropodine)} & & \text{(pteropodine)}\end{array} \arrow[d, shift right] \\
\begin{array}{c}\textit{epiallo}\text{ indole}\\ \text{(akuammigine)}\end{array} \arrow[r, rightleftharpoons] \arrow[u, shift right] & \begin{array}{ccc}\textit{epiallo}\text{ oxindole A} & \text{and} & \textit{epiallo}\text{ oxindole B}\\ \text{(speciophylline)} & & \text{(uncarine F)}\end{array} \arrow[u, shift right]
\end{tikzcd}$$