MEGHNAD SAHA MEMORIAL LECTURE, 1975

CHEMICAL STUDIES ON INDIAN PLANTS

by T. R. GOVINDACHARI, F.N.A., *Director, CIBA-GEIGY Research Centre, Goregaon East, Bombay-400063*

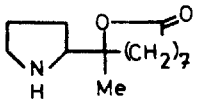
(*Delivered 2 January 1975*)

I am deeply conscious of the great honour done to me by the Indian National Science Academy in awarding the Meghnad Saha Medal for 1975. Professor Meghnad Saha was not only one of India's great scientists, but also a man endowed with a burning social conscience and I take pride in being even remotely connected to such a man, through this award.

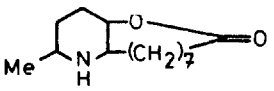
The chemical study of plants has been a favourite topic of research for several decades with a significant proportion of organic chemists in India. Some of the factors influencing this choice are the rich flora of India, with some 20,000 species of higher plants, the relative ease of collection, the medicinal importance claimed for many plants, the hope of discovering new therapeutic principles and above all the perennial fascination of the subject and the intellectual challenge it offers. Important contributions have been made in this country which have won international recognition. Special mention should be made of the work of Prof. T. R. Seshadri, Prof. K. Venkataraman, Prof. S. C. Bhattacharyya, Dr. Sukh Dev and Prof. Asima Chatterjee. I shall however restrict myself in this lecture to the work carried out by my associates and myself at Presidency College, Madras and later at the CIBA Research Centre, Bombay, during the last 25 years. I hope to be able to highlight some of our contributions in the elucidation of structure of some alkaloids, terpenoids and oxygen heterocycles isolated from Indian plants.

ALKALOIDS

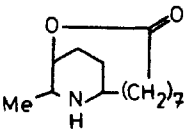
1. *Carpaine and Pseudocarpaine :* The alkaloid carpaine, isolated from *Carica papaya* L., was first assigned the structure (1) by Barger *et al.*. (1937). Rapoport and Baldridge (1951) obtained myristic acid by a two-stage Hofmann degradation of carpaine proving that this structure was untenable. Our own studies on carpaine were at first centred on the constitution of ethyl carpyrinate (cf. Govindachari & Narasimhan 1953; and Govindachari *et al.* 1957 *a*) obtained by dehydrogenation of ethyl carpamate. The ultra-violet spectrum of ethyl carpyrinate showed it to be a 3-hydroxy-pyridine, leading to two possible structures (2) and (3) for carpaine. The ethoxycarbonyl group of ethyl carpyrinate was replaced by a methyl group by a long sequence of reactions. Oxidation of the product gave an acid which was decarboxylated to 5-methoxy-2- octylpyridine. This led to structure (4) for ethyl carpyrinate, (5) for ethyl carpamate and (3) for carpaine.



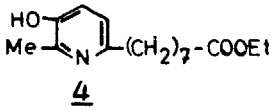
1



2

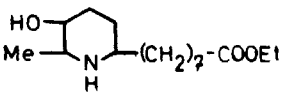


3



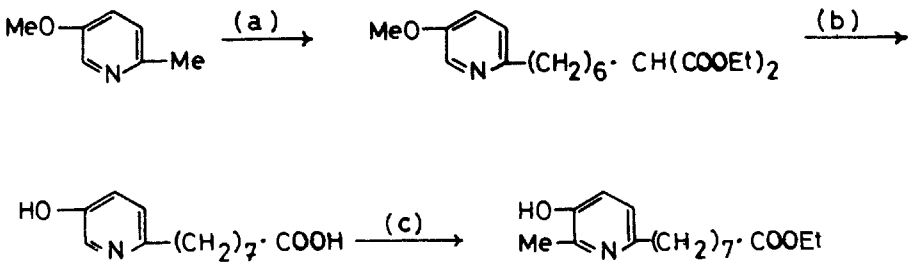
4

Ethyl carpyrinate



5 Ethyl carpamate

The structure of ethyl carpyrinate was confirmed by a synthesis (Govindachari *et al.* 1957 *b*).



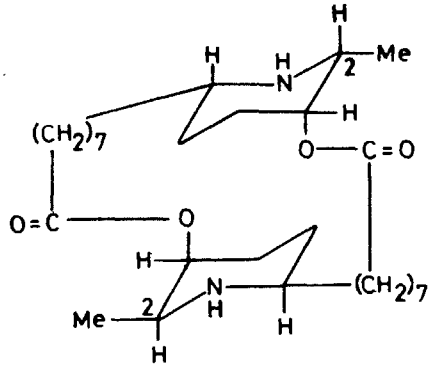
(a) 1. KNH_2-$Cl(CH_2)_5OAc$ 2. $LiAlH_4$ 3. $SOCl_2$ 4. $Na^+[CH(COOEt)_2]^-$

(b) HBr

(c) 1. HCHO–NaOH 2. EtOH-HCl 3. $SOCl_2$ 4. Pt-H_2 5. Pd-C

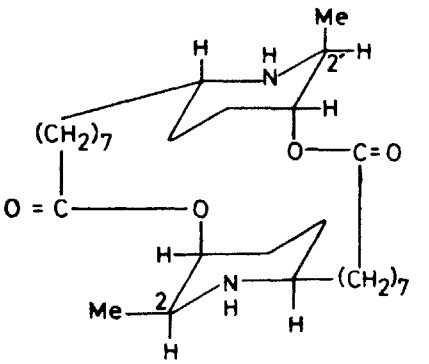
Many years later, carpaine was shown to have the dimeric structure (6) by Spiteller and Spiteller (1964) on the basis of mass spectral studies.

Pseudocarpaine, a minor alkaloid from the plant, had been shown to give on hydrolysis carpamic acid and an isomer pseudocarpamic acid (cf. Govindachari *et al.* 1954 *b*). Pseudocarpaine was considered to be epimeric with carpaine at C-3. Reinvestigation of its mass spectrum (M^+ at m/e 478) showed that pseudocarpaine also is a dimer. The C_2, C_6 groups in carpaine had to be *cis* since hydrogenation of deoxycarpyrinic acid followed by esterification gave ethyl deoxycarpamate (cf. Govindachari & Narasimhan 1955). A careful analysis of the 100 MHz N×R spectra of carpaine and pseudocarpaine led to the relative stereochemistry shown in formulae (6) and (7) for carpaine and pseudocarpaine respectively (cf. Govindachari *et al.* 1965).



6

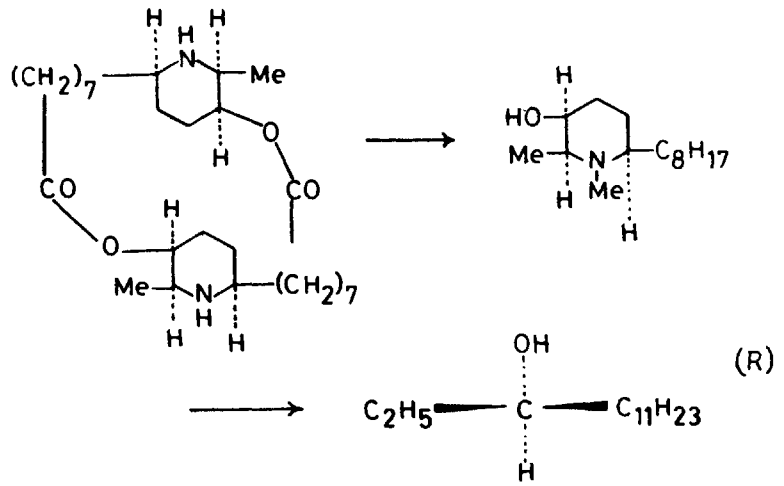
Carpaine



7

Pseudocarpaine

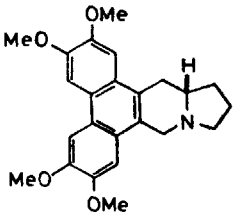
The absolute configuration according to Coke and Rice (1965) of carpaine has been shown to be as represented below by degradation to (R) (—)-3-tetradecanol.



2. *Alkaloids of Tylophora asthmatica :* The chemistry of the alkaloids of *Tylophora asthmatica* (*Asclepiadaceae*), which possess the novel phenanthroindolizidine ring system, has been reviewed before by Govindachari (1967, 1973). Two major alkaloids, tylophorine and tylophorinine and several minor ones were isolated and their structures established.

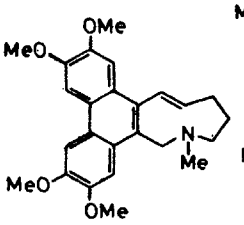
The structure of tylophorine (8) was deduced by extensive chemical degradation by Govindachari *et al.* (1954 *a*, 1958 and 1960). The alkaloid, $C_{24}H_{27}NO_4$, is a tertiary base having four methoxyl groups but no N-methyl group. Its ultraviolet

spectrum indicated a phenanthrene chromophore. Successive Hofmann degradations gave the methines (9) and (10). Emde degradation gave (11) which on dehydrogenation gave the pyrrole derivative (12) indicating a five-membered nitrogen-containing ring in the alkaloid.

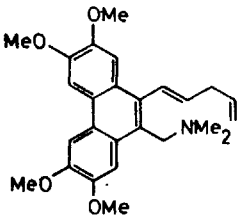


8

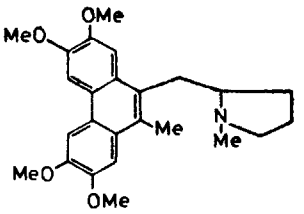
Tylophorine



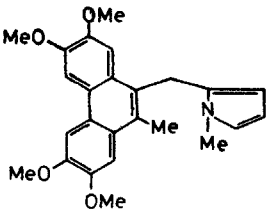
9



10

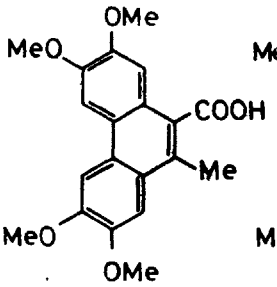


11

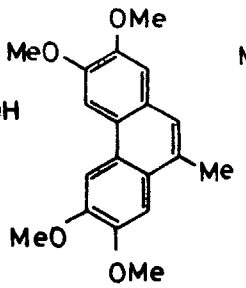


12

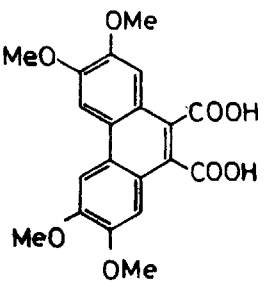
The Emde base (11) on Hofmann degradation followed by oxidation, gave the monoacid (13), decarboxylated to the phenanthrene (14), and the diacid (15) identical with a synthetic sample.



13

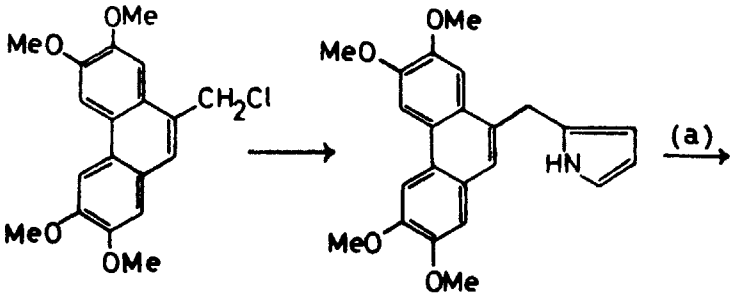


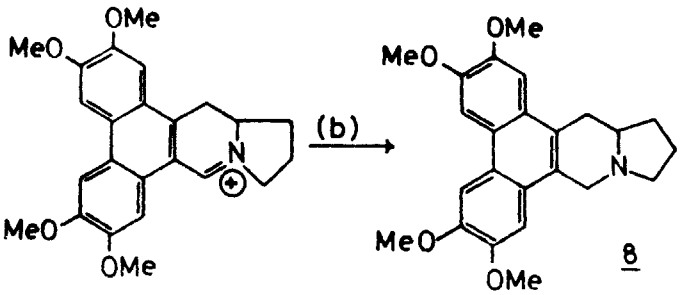
14



15

These and other degradative studies led to formula (8) for tylophorine. This was confirmed by a synthesis by Govindachari *et al.* (1961 *a*) outlined below:



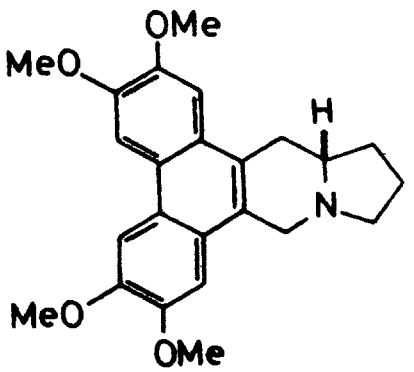


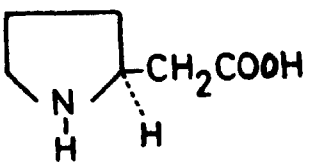
8

(a) 1. $Pt-H_2$ 2. HCOOH 3. $POCl_3$

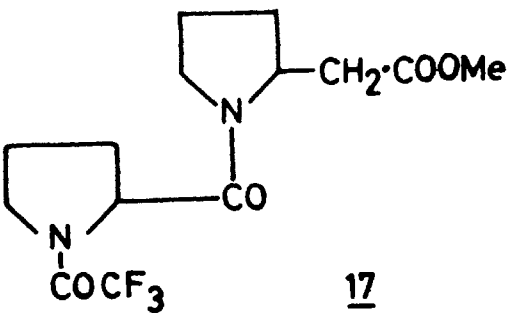
(b) $NaBH_4$

The absolute configuration at C-13 *a* of tylophorine was settled only recently (cf. Govindachari *et al.* 1974*a*). Ozonolysis of tylophorine gave *S*-2-pyrrolidine acetic





16

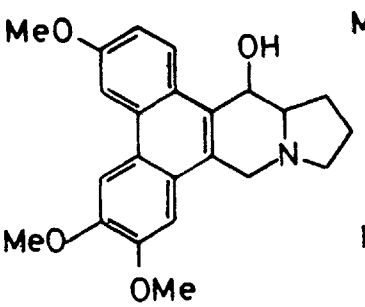


17

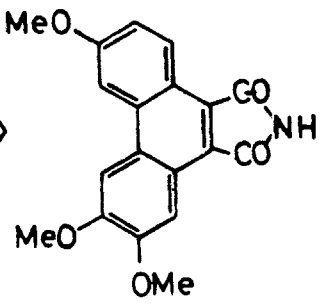
acid (16), identical with a sample synthesized from *S*-proline. Because of the minute amounts of the acid isolated from the ozonolysis, its identity was established by g.c. studies on the dipeptide (17) derived from its methyl ester.

Since tylophorine, having the *S* configuration at C-13 *a*, has a negative *Cotton Effect* in the region 200–280 *nm*, the configuration of other alkaloids of the group can be deduced from their o.r.d.

Tylophorinine (18), $C_{23}H_{25}NO_4$, is a tertiary base with three methoxyl groups and a secondary alcoholic hydroxyl group. Oxidation of the methiodide gave the imide (19) identical with a synthetic sample. Catalytic hydrogenation gave desoxytylophorinine which was shown to be (20) by syntheses of both (20) and (21). Since the hydroxyl was benzylic in view of the easy hydrogenolysis and since tylophorinine is not a carbinolamine, structure (18) follows for tylophorinine as given by Govindachari *et al.* (1961 *b*).

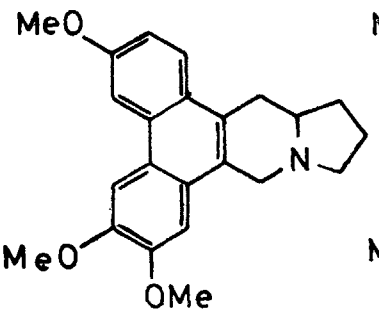


18

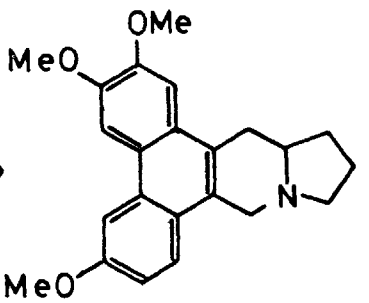


19

Tylophorinine



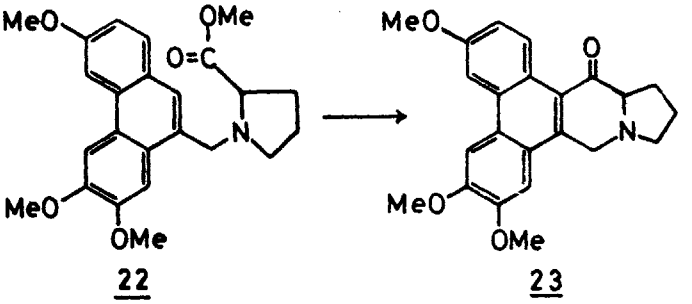
20

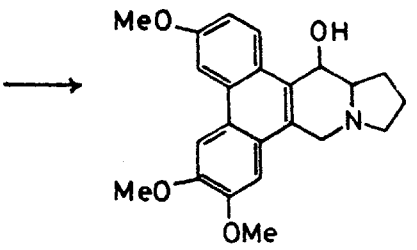


21

Desoxytylophorinine

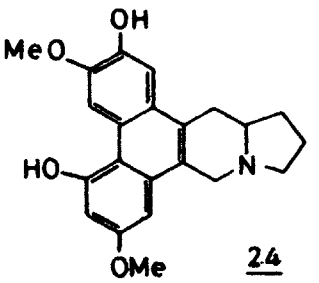
This was confirmed by synthesis (cf. Govindachari *et al.* 1965*a*) of the alkaloid through the intermediates (22) and (23).



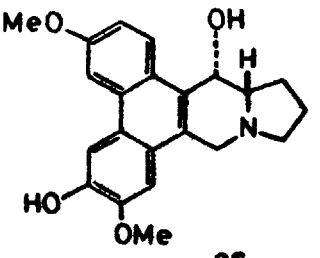


Tylophorinine

Tylophorinidine, one of the minor alkaloids, had been assigned structure (24) by Mulchandani *et al.* (1971). Our investigations led to the revision of its structure to (25), *O*-methyltylophorinidine being diastereoisomeric with tylophorinine (26) (Govindachari *et al.* 1973 *a*).

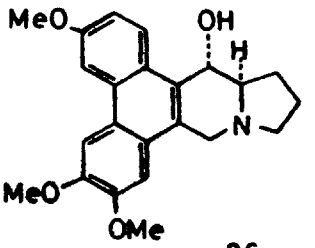


24



25

Tylophorinidine

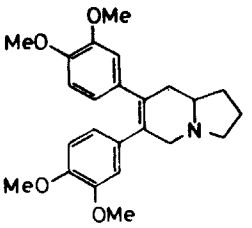


26

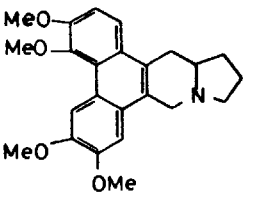
Tylophorinine

The structure and stereochemistry of tylophorinidine have been confirmed by an X-ray study of the methiodine of its diacetyl derivative (cf. Wadhawan *et al.* 1973 *a*).

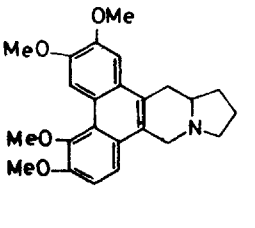
Two other minor alkaloids obtained from *T. asthmatica* were found to be d-septicine (27) and isotylocrebrine (28). Structure (29) had earlier been assigned to tylocrebrine, (cf. Gellert *et al.* 1962), isolated from *T. crebriflora*. Both compounds (28) and (29) were synthesized by the method developed for the synthesis of tylophorine.



27
Septicine

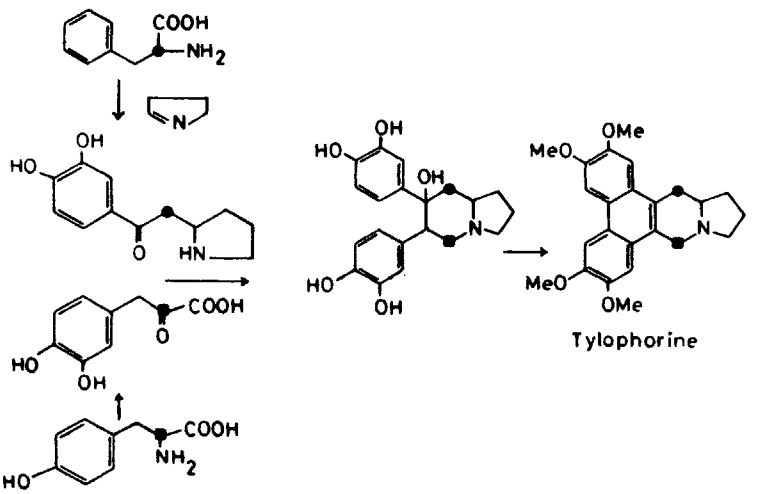


28
Isotylocrebrine



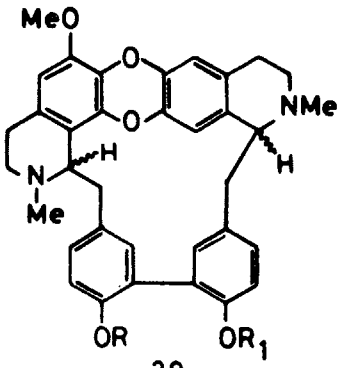
29
Tylocrebrine

As a result of recent biosynthetic work (cf. Mulchandani *et al.* 1969 and 1971), the scheme outlined below has been proposed for the biosynthesis of tylophorine. Tyrosine and phenylalanine are incorporated by separate pathways. The Δ^1-pyrroline unit is derived from ornithine.



Shivpuri *et al.* (1969) have found that the leaves of *T. asthmatica* are effective in the treatment of bronchial asthma. Tylophorine does not seem to be the active principle. Tylocrebrine shows high activity against lymphoid leukemia according to Gellert and Rudzats (1964). Unexpected central nervous system toxicity shown in the clinic resulted in the drug's withdrawal from tests.

3. *Alkaloids of Tiliacora racemosa* : Intermolecular oxidative coupling of two phenolic benzyliosquinolines lead to bisbenzyliosquinoline alkaloids. From *Tiliacora racemosa* Colebr. (*Menispermaceae*), we isolated four such alkaloids having a dibenzo-*p*-dioxin ring system. The two major alkaloids were tiliacorine (30) and its diastereoisomer tiliacorinine. The two minor alkaloids were shown to be isomeric *N*-nortiliacorinines (cf. Anjaneyulu *et al.* 1969).

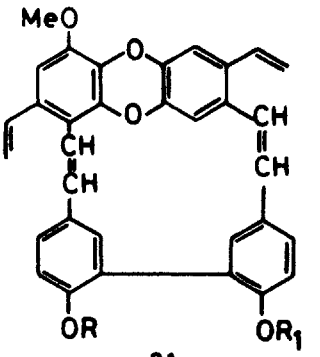


30

R=Me, R_1=H or vice versa

Tiliacorine

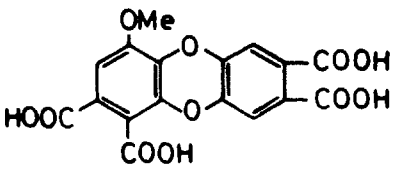
Tiliacorinine



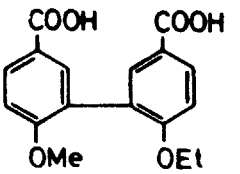
31

R=Me, R_1=Et

or vice versa



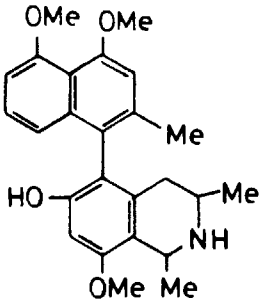
32



33

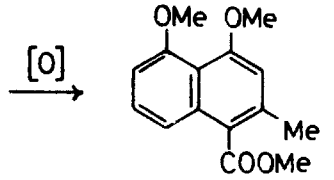
Tiliacorine and tiliacorinine were interrelated by a two-stage Hofmann degradation of their *O*-ethyl ethers to the same optically inactive methine (31). Oxidation of both *O*-ethyltiliacorine and *O*-ethyltiliacorinine gave the tetracarboxylic acid (32) and the dicarboxylic acid (33), both of which were identified by synthesis. The position of the phenolic hydroxyl as well as the absolute configurations of these alkaloids have not been settled yet mainly because there is no way of breaking the molecule into recognisable fragments. These alkaloids are unique in having a 2, 2′-dioxygenated diphenyl moiety instead of the usual diphenyl ether and arise in nature by the C-C pairing of two phenoxy radicals. The structure of *O*-methyltiliacorine has been confirmed by a total synthesis (cf. Anjaneyulu *et al.* 1971).

4. *Alkaloids of Ancistrocladus heyneanus :* A novel group of isoquinoline alkaloids has been isolated from *Ancistrocladus heyneanus* (*Ancistrocladaceae*). The major alkaloid, ancistrocladine, $C_{25}H_{29}O_4N$, was shown to have structure (34)

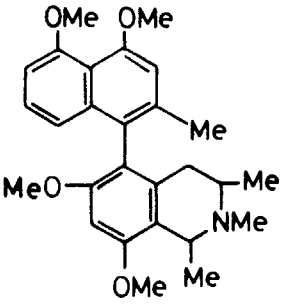


34

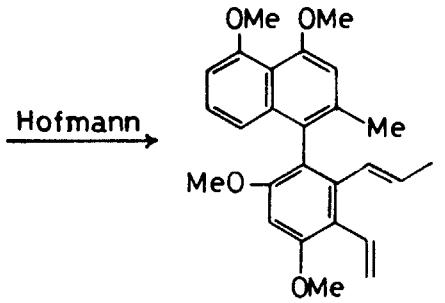
Ancistrocladine



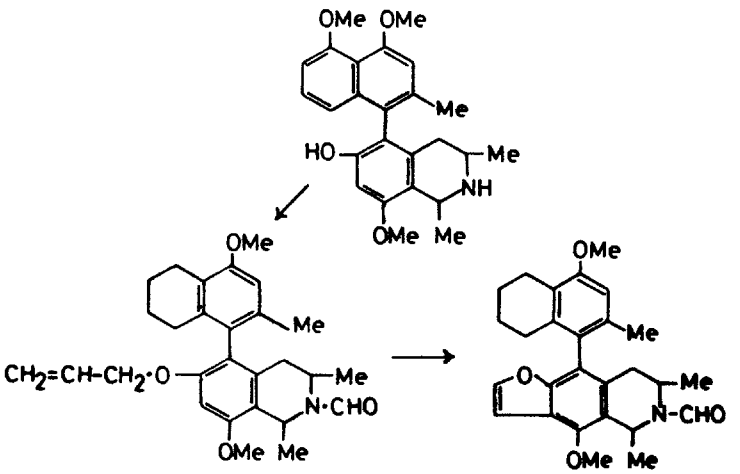
35



36



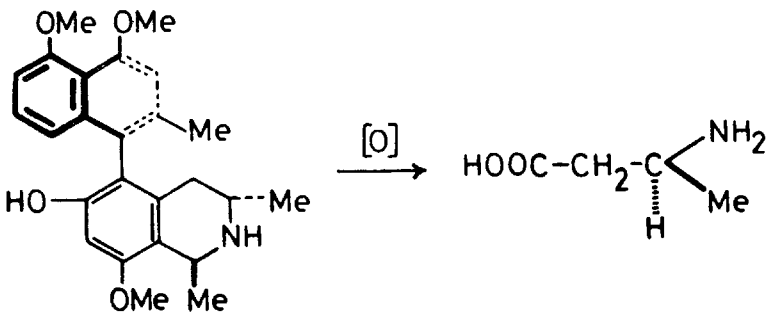
37



38 39

by extensive chemical degradation according to Govindachari and Parthasarthi (1971) and Govindachari *et al.* (1971 *a*). Ancistrocladine, on oxidation followed by methylation, yielded the ester (35). Hofmann degradation of O, N-dimethyl-ancistrocladine (36) to compound (37) indicated the presence of a 1, 3-dimethyltetrahydroisoquinoline ring and a naphthalene attached to C-5. The significant shielding of the methoxyl and acetate groups in the methyl ether and acetate of the base necessitates the placement of the phenolic hydroxyl at C-6. The third methoxyl is located at C-8 since Claisen rearrangement of O-allyl N-formyl-desmethoxytetrahydroancistrocladine (38) followed by ozonolysis of the product gave the benzofuran (39).

The relative stereochemistry of the methyl groups at C-1 and C-3 was shown to be *trans* by comparison of the NMR spectrum of 0-methylancistrocladine with model compounds. The gross structure as well as the relative positions of the methyl groups at C-1 and C-2′ were established by Dr. Kartha, Buffalo, by an X-ray study of the hydrobromide of ancistrocladine. In association with Dr. K. Nakanishi of Columbia University, we have established the absolute configuration of ancistrocladine arising from the restricted rotation of the C-5—C-1′ bond. This method is based on the circular dichroism study of the derived isoquinoline in which the asymmetric centres at C-1 and C-3 are destroyed. Coupled with the X-ray and chemical studies, ancistrocladine can be represented by structure (40). This has been confirmed by exhaustive ozonolysis of ancistrocladine to give L(+) —β-amino-*n*-butyric acid (S) identical with a synthetic sample made by Govindachari *et al.* (1974).

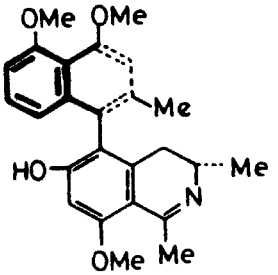


40 41

The structures of three other related alkaloids (cf. Govindachari *et al.* 1971 *b*, 1972 and 1973 *b*) isolated in minor amounts from the plant are depicted below (42, 43, and 44).

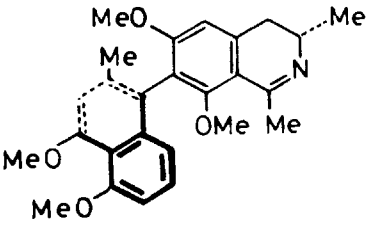
Hamatine, as given in an unpublished work of the author *et al.*, isolated from *Ancistrocladus hamatus,* a species found in Sri Lanka, has been found to have structure 45.

The pattern of methoxy substitution in ancistrocladine and its congeners fits in remarkably with the biogenetic origin of the alkaloids from 'polyketide' units.



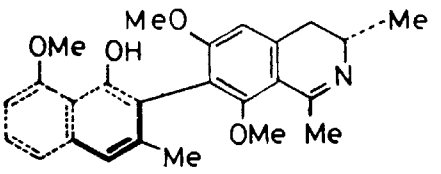
42

Ancistrocladinine



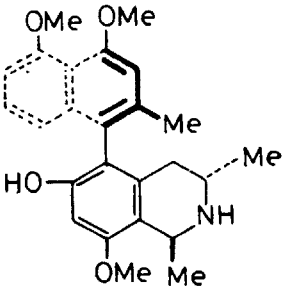
43

Ancistrocladisine



44

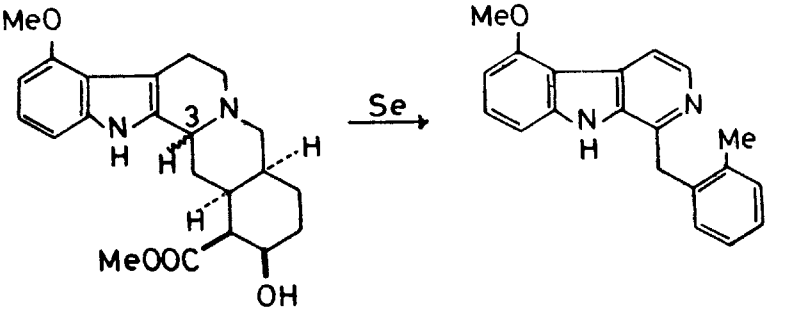
Ancistrocladidine



45

Hamatine

5. *Venenatine, Isovenenatine :* During the course of routine pharmacological screening we observed marked transquillising activity for the crude alkaloid isolated from the bark of *A. venenata.* The excitement however proved shortlived when the activity was traced to the presence of reserpine in the crude product. Besides



46 47

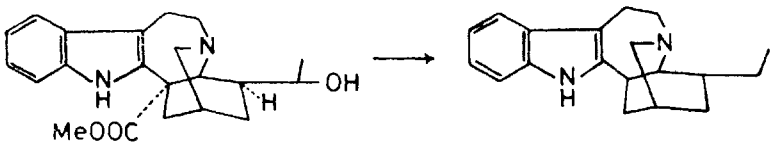
(a): C_3-β-H Venenatine

(b): C_3-α-H Isovenenatine

reserpine we isolated the known alkaloid kopsinine and two new indole alkaloids venenatine (46a) and its C-3 epimer, isovenenatine (46b) (Govindachari *et al.* 1965 *e*). Both the alkaloids contained a secondary hydroxyl and a carbomethoxy group and were inter-related by oxidation-reduction. The position of the methoxyl, assigned on the basis of ultraviolet and NMR spectra, was confirmed by dehydrogenation of venenatic acid to 5-methoxyyobyrine (47) identical with a synthetic sample (Govindachari *et al.* 1965 *d*).

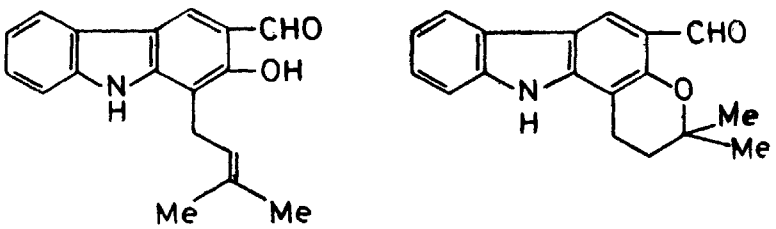
Mrs. Chatterjee and co-workers in a thorough investigation of other parts of the tree, isolated venenatine *N*-oxide, several alkaloids of the aspidospermine skeleton and the monoterpene alkaloid venoterpine.

6. *Heyneanine :* The roots and bark of *Tabernaemontana heyneana* (*Apocynaceae*) yielded a new indole alkaloid, heyneanine (48 a) (cf. Govindachari *et al.* 1966). The alkaloid, $C_{21}H_{26}N_2O_3$, has a secondary hydroxyl and a carbomethoxy group. Structure (48a) assigned on the basis of mass and NMR spectral studies, was confirmed by chemical correlation with the known alkaloid ibogamine (48b).



48 a Heyneanine — 48 b Ibogamine

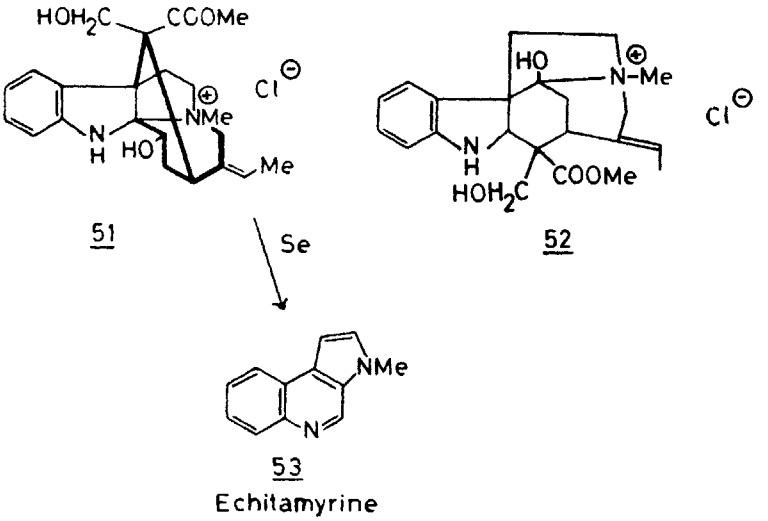
7. *Heptaphylline :* From *Clausena heptaphylla* (*Rutaceae*) we isolated a weakly basic carbazole alkaloid, heptaphylline (49) (cf. Joshi *et al.* 1972). The ultraviolet spectrum of the alkaloid is characteristic of 3-formyl carbazoles. The presence of a, γ γ-dimethylallyl group was shown by NMR and confirmed by acid-catalysed cyclisation to cycloheptaphylline (50). The structure of heptaphylline was confirmed by synthesis from 2-hydroxy-3-formylcarbazole and 3, 3-dimethylallyl bromide.



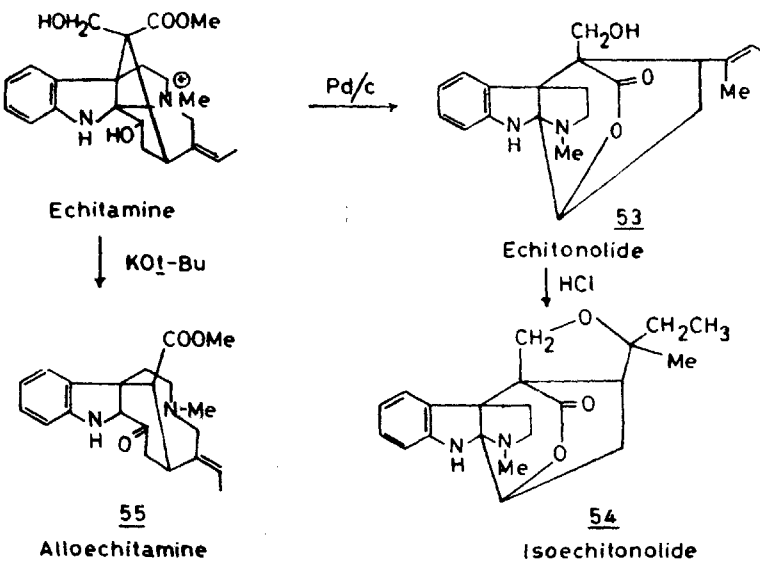
49 Heptaphylline — 50 Cycloheptaphylline

8. *Echitamine :* The dihydroindole alkaloid echitamine isolated as early as 1875 from *Alstonia scholaris* drew the attention of more than half a dozen research

groups. Several erroneous structures were suggested and the confusion was resolved only by X-ray studies (cf. Hamilton *et al.* 1961; and Manohar & Ramaseshan 1963) which led to the structure 51.



Among the incorrect structures proposed, special mention should be made of structure 52 proposed by Conroy *et al.* (1960) which seemed to account for most of the reactions of echitamine. This structure is a β-type dihydroindole and lacks the N_a-C-N_b system. Our own studies (cf. Govindachari & Rajappa 1961) on the ultraviolet spectra of echitamine and its degradation products showed the presence of an N_a-C-N_b system in the alkaloid. The ease of hydrogenolysis of the

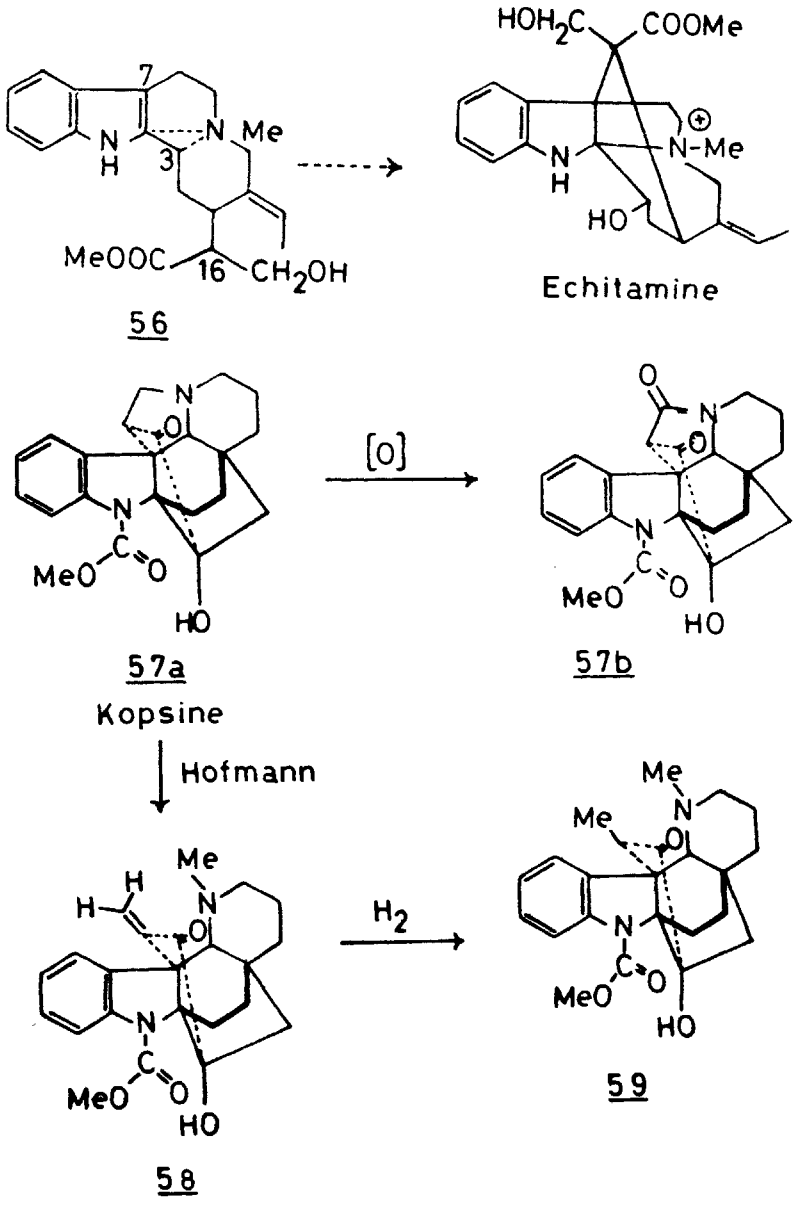


alkaloid established that it was an allyl quarternary ammonium salt. In an attempt to obtain a clue to the skeletal structure, the reduction product, echitonolide, was subjected to selenium dehydrogenation. The product, echitamyrine, was shown to have structure 53 by synthesis.

Echitamyrine could conceivably arise either from an α-or β-type dihydroindole alkaloid and did not therefore prove to be of value in the structure elucidation.

The key degradation products of echitamine, echitonolide, isoechitonolide and allo-echitamine (55), can be formulated as follows in the light of the correct structure.

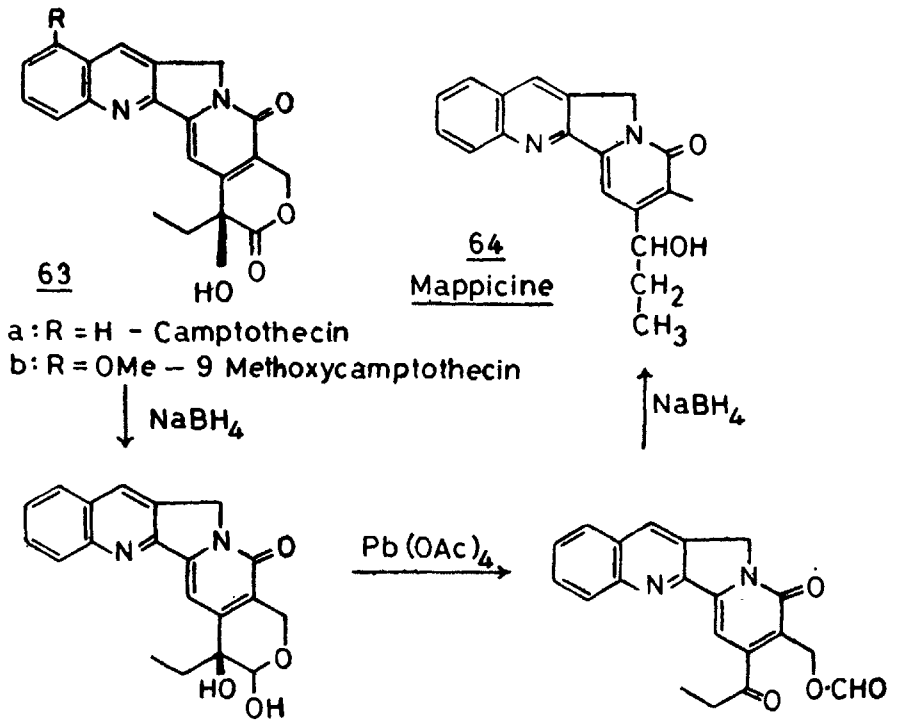
Echitamine can arise in nature from an intermediate of the type 56 derivable from a tryptamine and a secologanin unit. Oxidative coupling of C_{16} with C_7 in the indolenine form and formation of a N_b—C_2 bond would lead to echitamine. The hydroxyl group at C-3 is at a position compatible with this scheme.

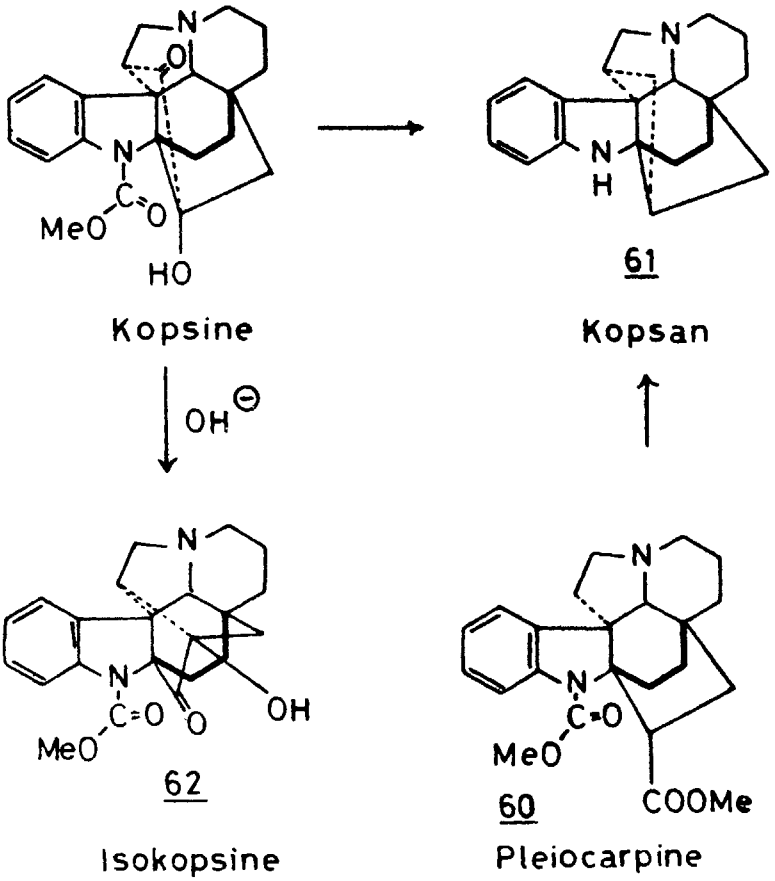


9. *Kopsine :* Chemical examination of *Kopsia fruticosa* (*Apocynaceae*) yielded five structurally related alkaloids of which kopsine is the major one. In collaboration with Prof. H. Schmid, Zurich University, we were able to derive structure 57a for kopsine (cf. Govindachari *et al.* 1963*a*, 1963*b*).

Kopsine, $C_{22}H_{24}N_2O_4$, has a 5-membered ring ketone, a tertiary hydroxyl and an N-COOMe group, thus accounting for all the oxygen atoms. Oxidation gave a lactam (57b). Hofmann degradation of kopsine methiodide gave the α, β-unsaturated ketone (58) which was reduced to the dihydroderivative (59). A study of the NMR spectra of these compounds indicated the structure 57a for kopsine. This was confirmed by a correlation with the known alkaloid pleiocarpine (60). Kopsinyl iodide prepared from pleiocarpine gave on pyrolysis in 60 per cent yield a product kopsan shown to have structure 61. By heating kopsine with red phosphorus and hydriodic acid, the same compound kopsan was obtained thus proving its skeletal structure. An interesting acyloin rearrangement occurs during the alkaline hydrolysis of kopsine. The product, isokopsine, has been shown to have structure 62 (See page 17).

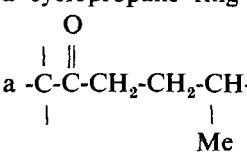
10. *Alkaloids of Mappia foetida :* In the course of routine investigations of plants for biological activity, we discovered a very convenient source (yield 0.1 per cent) for the antitumour alkaloid, camptothecin (63 a), which was hitherto available only from the rare Chinese tree, *Camptotheca acuminata* in low yield (0.005 per cent). The tree, *Mappia foetida,* is abundant in India and contains as minor constituents 9-methoxycamptothecin (Govindachari & Viswanathan 1972) (63b) and mappicine (Govindachari *et al.* 1974*b*) (64). The latter was chemically correlated with camptothecin as shown below :





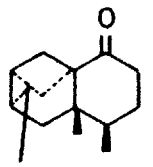
TERPENOIDS

1. *Ishwarone :* Ishwarone (65), isolated in 1935 from *Aristolochia indica* (*Aristolochiaceae*) by Rao *et al.* (1935), was shown by extensive chemical degradation to be a novel tetracyclic sesquiterpene (cf. Führer *et al.* 1970). Ishwarone, $C_{15}H_{22}O$, has a six membered ketone group, one secondary C-Me, two secondary C-Me and a cyclopropane ring which could be opened by acid treatment. The

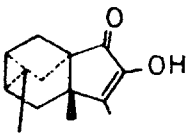


presence of a -C-C-CH_2-CH_2-CH- system was shown by ring contraction to norish-

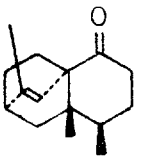
warone and subsequent Barton oxidation to the diosphenol (66) which showed the olefinic C-Me at δ 1.87 in the NMR spectrum.



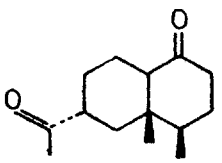
65
Ishwarone



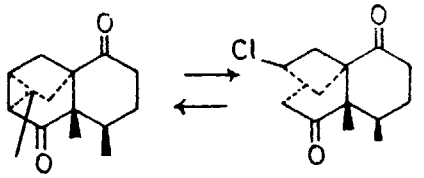
66



67



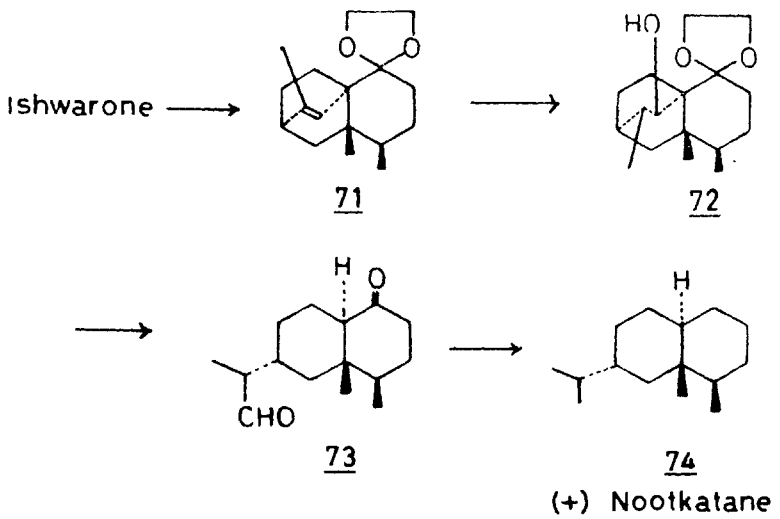
68



69 70

Isoishwarone (67), obtained from ishwarone by acid treatment, was ozonised to give the diketone 68 identical with an authentic sample prepared from valerianol. Treatment of ishwarone with ozone resulted in oxidation of a methylene adjacent to the cyclopropane ring to oxoishwarone (69). With hydrochloric acid this gives the chloro compound (70) which reverts to oxoishwarone with pyridine.

The absolute configuration of ishwarone was derived by chemical correlation with (+)-nootkatane. The ethylene-ketal (71) of isoishwarone, on hydroboration and oxidation gave the alcohol (72). Deketalisation and alkali-induced retro-aldolisation of the resultant aldol gave the ketoaldehyde (73). Wolff-Kishner reduction of this gave (+)-nootkatane (74) identical with an authentic sample.

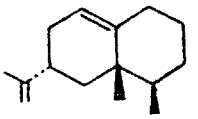


71 72 73 74
(+) Nootkatane

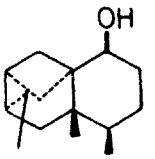
Besides ishwarone, four other sesquiterpenes (cf. Govindachari *et al.* 1970, 1973*b* : and Govindachari & Parthasarathi 1971*a*) were isolated from *A. indica* and shown to have structures 75–78.

Other sesquiterpenes of A. indica

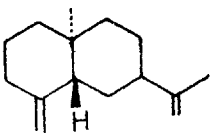
75
Ishwarane



76
Aristolochene

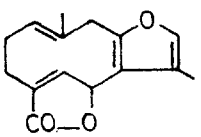


77
Ishwarol

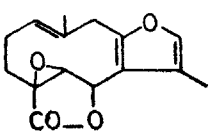


78
Selinadiene

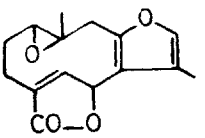
2. *Sesquiterpenes of Neolitsea zeylanica* : From *Neolitsea zeylanica* (*Lauraceae*) we isolated six new furano-germacronolides and deduced their structures 79–84 mainly on the basis of their spectra (Joshi *et al.* 1967 *a*, *b* and *c*).



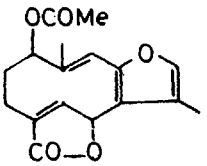
79
Linderalactone



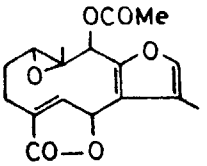
80
Linderane



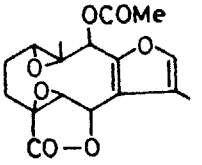
81
Neolinderane



82
Zeylanine

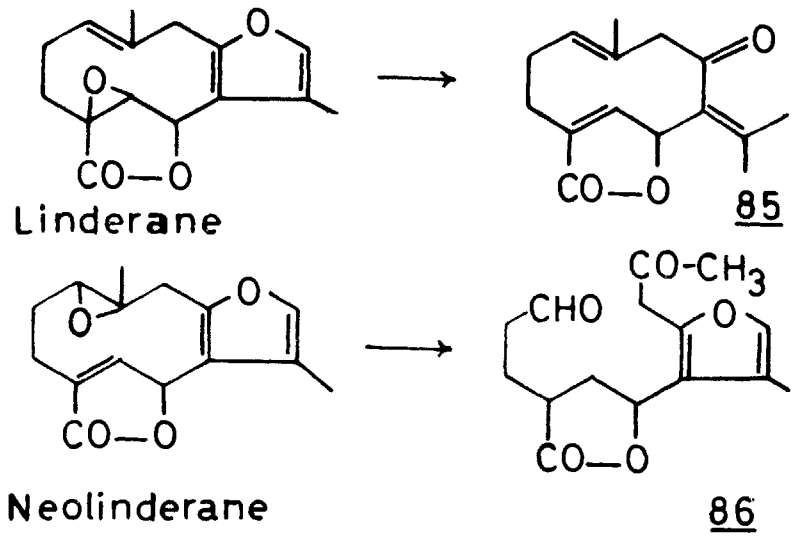


83
Zeylanicine



84
Zeylanidine

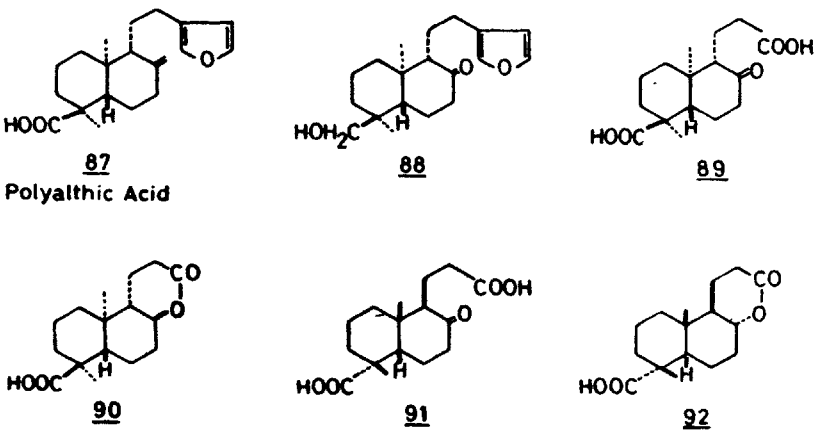
Deoxygenation of 80 by chromous chloride gave 79 and an interesting by-product 85. Deoxygenation of 84 gave 83.



The structure of neolinderane (81) was proved by opening of the epoxide to the corresponding diol and cleavage to the keto-aldehyde (86).

3. *Polyalthic Acid :* Polyalthic acid according to Gopinath *et al.* (1961*a*), isolated from *Polyalthia fragrans* (*Anonaceae*), was proved to have structure 87 by degradation.

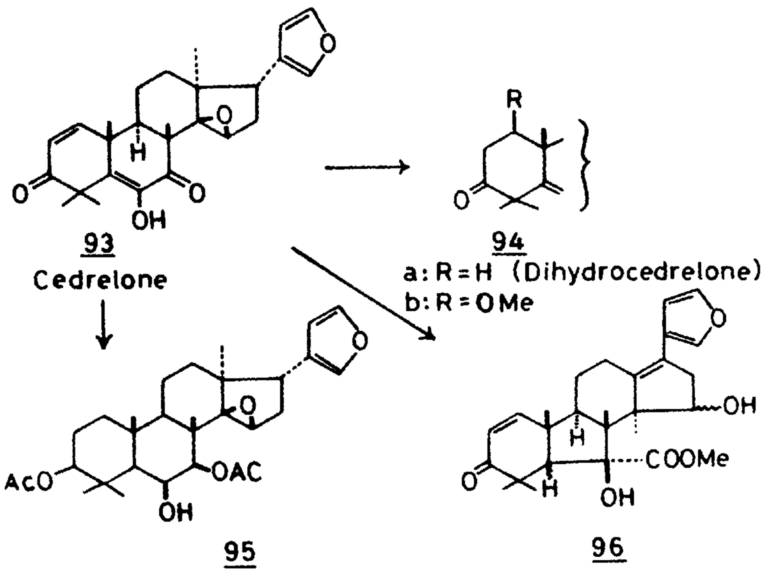
The acid, $C_{20}H_{28}O_3$, was found to have a hindered carboxyl, an exocyclic methylene, a β-monosubstituted furan ring and two tertiary C-Me groups. Osmylation of polyalthyl alcohol followed by cleavage gave the keto-alcohol 88, having an infrared band at 5.85 μ (six-membered ketone).



Ozonolysis of the acid gave the keto-dicarboxylic acid (89) which was reduced by sodium borohydride to the lactone-acid (90). Compounds 89 and 90 proved

to be the antipodes of acids (91) and (92) respectively which were prepared from neoabietic acid.

4. *Cedrelone* : Chemical and spectral investigations combined with biogenetic arguments led to structure 93 for cedrelone (Gopinath *et al.* 1971*b*) the bitter principle of *Cedrela toona*. The structure was established (apart from absolute configuration) by an X-ray study carried out by Grant *et al.* (1961).



Mass spectral studies led to revision of its formula from $C_{25}H_{30}O_5$ to $C_{26}H_{30}O_5$. Two of the oxygen atoms must be located in a diosphenol system as shown by its ultraviolet spectrum and formation of a monoacetate and monomethyl ether. The NMR spectrum of cedrelone showed the presence of five tertiary C-Me groups, a β-monosubstituted furan ring, an enone chromophore of the type -C-C-CH=CH-C-C (with C=O on the second carbon and two C substituents on the fifth carbon)

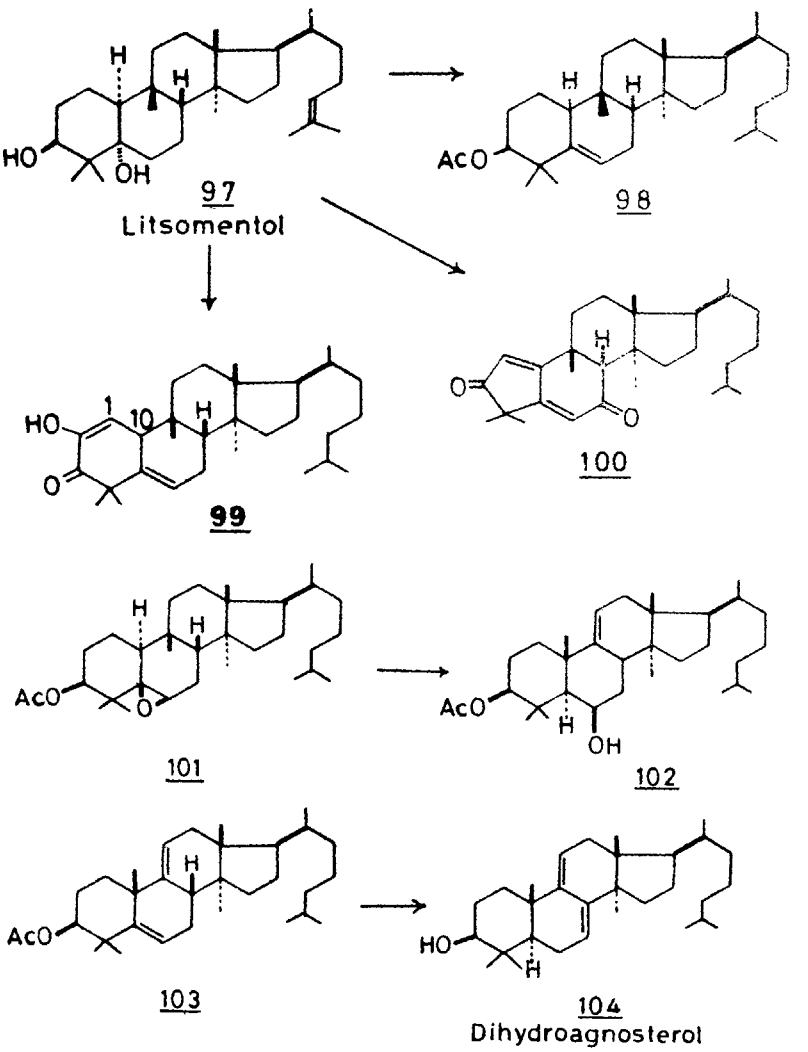
and an epoxide hydrogen. Mild reduction of cedrelone with sodium borohydride gave the dihydro-derivative (94a) while base-catalysed addition of methanol gave (94b). Drastic reduction with sodium borohydride followed by acetylation gave the diacetate (95). On treatment with alkali, cedrelone undergoes a facile benzilic acid rearrangement to yield an acid $C_{26}H_{32}O_6$ characterised as the methyl ester (96), having a new chromophore (λ_{max} 242 *nm*, ϵ 13500 after correction for the enone chromophore). The structural features of cedrelone were reminescent of limonin and led to structure 93 as the most likely one.

5. *Litsomentol* : From the bark of *Litsea tomentosa* (*Lauraceae*) we isolated a triterpene, litsomentol (97), (Govindachari *et al.* 1971*c*), which proved to be the simplest member of the cucurbitacin group. It is unique in lacking an oxygen

function at C-11 and in being the only member of the group isolated from a plant belonging to the *Lauraceae* family.

Litsomentol, $C_{30}H_{52}O_3$, has a secondary hydroxyl group (formation of acetate and ketone), a tertiary hydroxyl (dehydration to anhydro-derivative) and a tri-substituted double bond (reduction to dihydro, epoxidation to mono--epoxide). The double bond is situated on the side chain since ozonolysis gives acetone and a trisnor-acid.

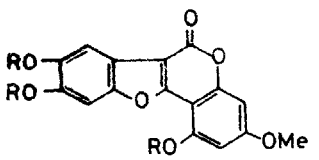
The presence of a hydrogen at C-10 is shown by coversion of acetylanhydro-dihydrolitsomentol (98) to the diosphenol (99) in which the C_1—H appears as a doublet at δ 6.12 (J 2.5 Hz). The mass spectral fragmentation of litsomentol and its derivatives support structure 97. The location of the hydroxyl groups was confirmed by degradation to the dienedione (100) (λ_{max} 286 *nm* log ϵ 4.33).



The structure and stereochemistry of litsomentol were confirmed by chemical correlation involving a rearrangement of the cucurbitacin to the lanosterol skeleton by a backbone rearrangement. Acetylanhydrodihydrolitsomentol (98) was epoxidised to (101) which rearranged with boron trifluoride etherate to the alcohol (102). Treatment of 102 with methane-sulphonyl chloride and pyridine gave the unconjugated diene (103). The latter, when refluxed with N-lithioethylenediamine, underwent isomerisation and hydrolysis to yield dihydroagnosterol (104) identical with an authentic sample.

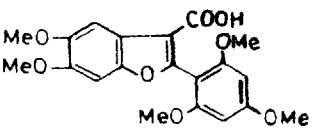
Oxygen Heterocycles

1. *Wedelolactone :* From *Wedelia calendulaceae* (*Compositae*), a plant reputed to be useful in the treatment of jaundice, we isolated a lactone, wedelolactone Govindachari *et al.* (1956, 1957*a*) (105a), which proved to be the first member of a novel ring system, the coumestans. Wedelolactone, $C_{16}H_{10}O_7$, has one methoxyl, three phenolic hydroxyls and an α, β-unsaturated δ-lactone group. Methylation gave the tri-0-methyl ether (105b). Hydrolysis of 105b, treatment of the resultant acid with diazomethane and rehydrolysis gave the acid 106.

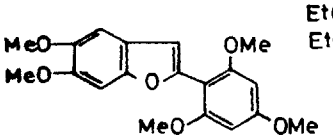


105

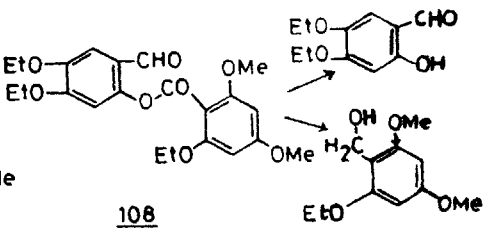
a: R = H – Wedelolactone
b: R = Me



106



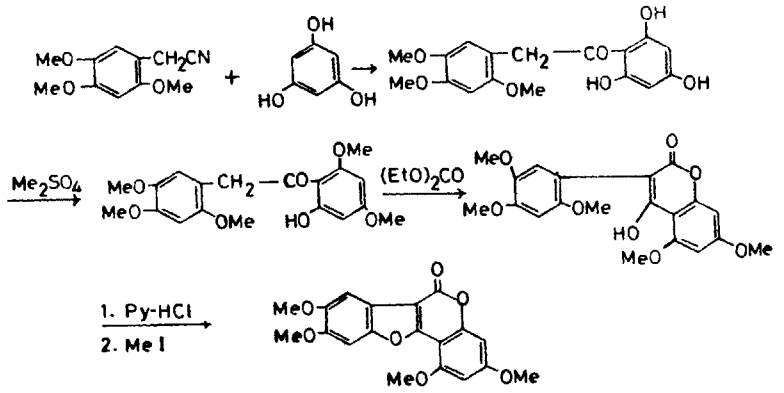
107



108

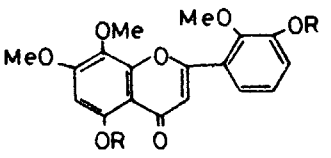
Decarboxylation of (106) gave the benzofuran (107). Ozonolysis of (107) and alkaline hydrolysis of the product gave 6-hydroxyveratraldehyde and 2, 4, 6-trimethoxybenzoic acid. The position of the methoxyl in wedelolactone was established by ethylation to a tri-0-ethylether followed by conversion to the ester (108). Hydrolysis of (108) gave 2-hydroxy-4, 5-diethoxybenzaldehyde while lithium aluminium hydride reduction gave 2-ethoxy-4, 6-dimethoxybenzyl alcohol.)

The synthesis (Govindachari *et al.* 1957*b*) of tri-0-methylwedelolactone (105b) was achieved by the route outlined as follows:



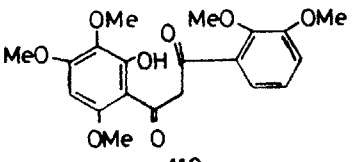
2. *Andrographis flavones :* From plants belonging to Andrographis species (*Acanthaceae*) we isolated a group of flavones with an unusual oxygenation pattern. These contain an oxygen, function at C-2′.

Wightin (Govindachari *et al.* 1965*b*) isolated from *Andrographis wightiana*, was shown to have structure 109a by spectral studies as well as degradation. The flavone, $C_{18}H_{16}O_7$, has three methoxyl groups and two phenolic hydroxyls one of which is chelated with a carbonyl.

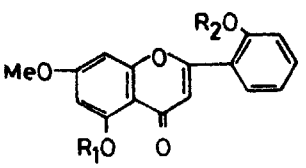


109

a: R=H – Wightin
b: R=Me
c: R=Et

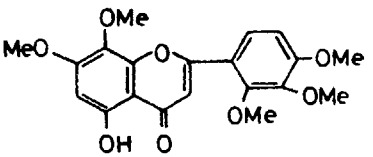


110



111

a : R_1= R_2 = H - Echioidinin
b: R_1= H, R_2= Glu-Echioidin



112

Serpyllin

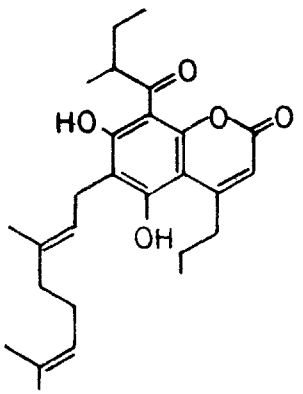
Hydrolysis of di-0-methylwightin (109b) gave wightinone (110) identical with a synthetic sample. The presence of a hydroxyl at C-5 in wightin was shown by shifts in its ultraviolet spectrum in the presence of aluminium chloride. The second hydroxyl was shown to be at C-3′ since di-0-ethylwightin (109c) gave

3-ethoxy-2-methoxybenzoic acid on oxidation. The synthesis of di-0-ethylwightin (109c) by the classical route confirms the structure assigned to wightin.

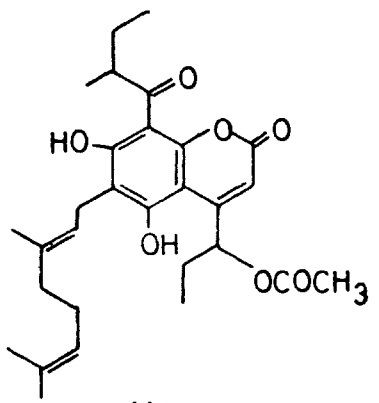
From *A. echioides*, a new flavone echioidinin (Govindachari *et al.* 1965*c*) and its glucoside echioidin (Govindachari *et al.* 1965*d*) were isolated. On the basis of spectral and degradative evidence, these were shown to have structures (111a) and (111b) respectively. The structure of echioidinin was confirmed by synthesis. Echioidin was shown to be echioidinin-2′-β-*D*-glucoside by degradation as well as by partial synthesis from echioidinin.

Serpyllin (Govindachari *et al.* 1968) isolated from *A. serpyllifolia,* was shown to be (112) by spectral and synthetic evidence.

3. *Coumarins of Mammea longifolia*—The roots of *Mammea longifolia* (*Guttiferae*) gave two coumarins (Joshi *et al.* 1969) surangin A and surangin B, which displayed high insecticidal activity against the house fly. The structures of these were derived as 113 and 114 respectively by spectral data without recourse to any degradation.



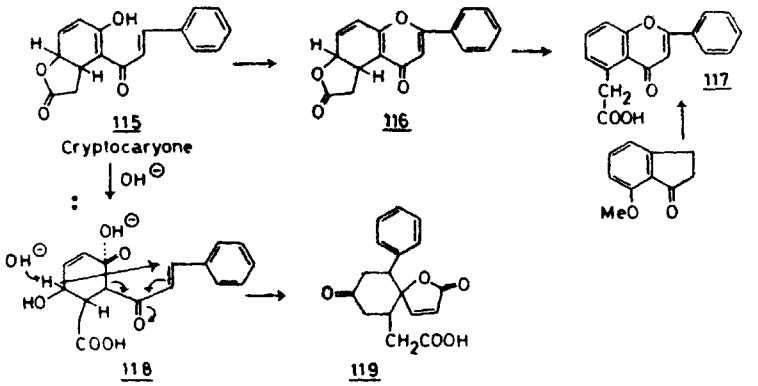
113
Surangin A



114
Surangin B

Their ultraviolet spectra showed them to be 5, 7-dihydroxy-coumarins with an acyl group at C-8. The NMR and mass spectra furnished adequate evidence for the assignment of structures.

4. *Cryptocaryone :* From the roots of *Cryptocarya bourdilloni* (*Lauraceae*), we isolated cryptocaryone (Govindachari *et. al.* 1973*c*) (115), a novel 5′, 6′-dihydrochalcone, the first of its kind to occur in nature. Cryptocaryone, $C_{17}H_{16}O_4$, exhibits spectral properties suggestive of the presence of a five-membered saturated lactone, an extended cinnamoyl chromophore and an enolized β-diketonic function. NMR studies led to structure (115). Treatment of cryptocaryone with selenium dioxide gave the 5, 6-dihydroflavone (116) which was isomerised to the flavone-carboxylic acid (117). The methyl ester of the acid was identical with an authentic sample synthesized from 7-methoxy-indan-1-one.



Cryptacaryone is extremely labile to alkali and gives the acid 119 presumably *via* the intermediate 118.

Acknowledgements

Whatever merit you find in the results I presented is largely due to the devoted labour, experimental skill and intellectual acumen of several of my co-workers. I should like to mention in particular, Prof. B. R. Pai, Dr (s). K. Nagarajan, N. Viswanathan and P. C. Parthasarathy who have been associated with me through most of my scientific career and thank them for their participation in these researches. Finally, I wish to thank the Indian National Science Academy for awarding me a medal for carrying out work which my colleagues and I have thoroughly enjoyed doing over the years.

References

Anjaneyulu, B., Govindachari, T. R., Sathe, S. S., Viswanathan, N., Gopinath, K. W., and Pai, B. R. (1969). Alkaloids of *Tiliacora racemosa* Colabr. *Tetrahedron*, **25**, 3091–3105.

Anjaneyulu, B., Govindachari, T. R., and Viswanathan, N. (1971). Total synthesis of dl-O-Methyl-tiliacorine. *Tetrahedron*, **27**, 439–443.

Barger, G., Robinson, R., and Work, T. S. (1937). Constitution of Carpaine, Part III. *J. chem. Soc.*, 711–713.

Coke, J. L., and Rice, W. Y. (1965). The absolute Configuration of Carpaine. *J. org. Chem.*, **30**, 3420–3422.

Conroy, H., Bernasconi, R., Brook, P. R., Ikan, R., Kurtz, R., and Robinson, K. W. (1960). The structure of Echitamine. *Tetrahedron Lett.*, No. 6, 1–9.

Führer, H., Ganguly, A. K., Gopinath, K. W., Govindachari, T. R. Nagarajan, K., Pai, B. R., and Parthasarathy, P. C. (1970). Ishwarone. *Tetrahedron*, **26**, 2371–2390.

Gellert, E., Govindachari, T. R., Lakshmikantham, M. V., Ragade, I. S., Rudzats, R., and Viswanathan, N. (1962). The Alkaloids of *Tylophore crebriflora* : Structure and synthesis of Tylocrebrine, a new phenanthroindolizidine alkaloid. *J. chem. Soc.*, 1008–1014.

Gellert, E., and Rudzats, R. (1964). The Antileukamia Activity of Tylocrebrine. *J. med. Chem.*, **7**, 361–362.

Gopinath, K. W., Govindachari, T. R., Parthasarathy, P. C., and Viswanathan, N. (1961*a*). Structure and stereochemistry of Polyalthic Acid, a new diterpene acid. *Helv. Chim. Acta*, **44**, 1040–1049.

Gopinath, K. W., Govindachari, T. R., Parthasarathy, P. C., Viswanathan, N., Arigoni, D., and Wildman, W. C. (1961*b*). The structure of Cedrelone. *Proc. chem. Soc.*, 446–447.

Govindachari, T. R. (1967). Tylophora Alkaloids in' *The Alkaloids'*, Ed. R. H. F. Manske, **9,** 517–528. Academic Press, New York.

———(1973). Tylophora Alkaloids. *J. Indian chem. Soc.*, **50,** 1–9.

Govindachari, T. R., Joshi, B. S., Saksena, A. K., Sathe, S. S., and Viswanathan, N. (1966). Correlation of Heyneanine with Ibogamine. *Chem. Comm.*, **97.**

Govindachari, T. R., Lakshmikantham, M. V., Nagarajan, K., and Pai, B. R. (1958). Chemical Examination of *Tylophora asthmatica*—II. *Tetrahedron*, **4,** 311–324.

Govindachari, T. R., Lakshmikantham, M. V., Pai, B. R., and Rajappa, S. (1960). Chemical Examination of *Tylophora asthmatica*—III. The complete structure of Tylophorine. *Tetrahedron*, **9,** 53–57.

Govindachari, T. R., Lakshmikantham, M. V., and Rajadurai, S. (1961*a*). Chemical Examination of *Tylophora asthmatica*—IV. Synthesis of Tylophorine. *Tetrahedron*, **14,** 284–287.

Govindachari, T. R., Mohamed, P. A., and Parthasarathy, P. C. (1970). *Ishwarone and Aristolochene*, two new sesquiterpene hydrocarbons from Aristolochia Indica. *Tetrahedron*, **26,** 615–619.

Govindachari, T. R., Nagarajan, K., and Pai, B. R. (1956). Chemical Examination of *Wedelia calenduloceae*. Part I. Structure of Wedelolactone. *J. chem. Soc.*, 629–632.

Govindachari, T. R., Nagarajan, K., Pai, B. R., and Parthasarathy, P.C. (1957*a*). Chemical Investigation of *Wedelia calendulaceae*. Part II. The position of the methoxyl group in E Wedelolactone. *J. Chem. Soc.*, 545–547.

Govindachari, T. R., Nagarajan, K., and Parthasarathy, P. C. (1957*b*). Chemical Examination of *Wedelia calendulaceae*. Part III. Synthesis of Tri-o-methyl wedelolactone. *J. Chem. Soc.*, 548–551.

Govindachari, T. R., Nagarajan, K., Parthasarathy, P. C., Rajagopalan, T. G., Desai, H. K., Kartha, G., Chen, S. L., and Nakanishi, K. (1974). Absolute stereochemistry of Ancistrocladine and Ancistrocladinine. *J. chem. Soc. Perkin I*, 1413–1417.

Govindachari, T. R., Nagarajan, K., and Schmid, H. (1963*a*). *Umlagerungs-reaktionen des Kopsins. Helv. Chim. Acta*, **46,** 433–444.

Govindachari, T. R., Nagarajan, K., and Viswanathan, N. (1965). Carpaine and pseudocarpaine. *Tetrahedron Lett.*, 1907–1916.

Govindachari, T. R., and Narasimhan, N. S. (1953). Constitution of Carpaine. *J. chem. Soc.*, 2635–2637.

————(1955). Stereochemistry of Carpamic Acid. *J. chem. Soc.*, 1563–1565.

Govindachari, T. R., Narasimhan, N. S., and Rajadurai, S. (1957*a*). Some Degradation Studies of Carpaine. *J. chem. Soc.*, 558–560.

————(1957*b*). Synthesis of Ethyl Carpyrinate. *J. chem. Soc.*, 560–563.

Govindachari, T. R., Pai, B. R., and Nagarajan, K. (1954 *a*). Chemical Examination of *Tylophora asthmatica*, Part I. *J. chem. Soc.*, 2801–2803.

Govindachari, T. R., Pai, B. R., and Narasimhan, N. S. (1954 *b*). Pseudocarpaine, a new alkaloid from *Carica papaya* L. *J. chem. Soc.*, 1847–1849.

Govindachari, T. R., Pai, B. R., Prabhakar, S., and Savitri, T. S. (1965 *a*). Synthesis of (±) Tylophorinine. *Tetrahedron*, **21,** 2573–2578.

Govindachari, T. R., Pai, B. R., Ragade, I. S., Rajappa, S., and Viswanathan, N. (1961*b*). Chemical Examination of *Tylophora asthmatica*—V. *Tetrahedron*, **14,** 288–295.

Govindachari, T. R., Pai, B. R., Rajappa, S., Viswanathan, N., Kump, W. G., Nagarajan, K., and Schmid, H. (1963*a*). *Uder die Struktur des Kopsins. Helv. Chim. Acta*, **46,** 572–577.

Govindachari, T. R., and Parthasarathy, P. C. (1971). Ancistrocladine, a new type of isoquinoline alkaloid from *Ancistrocladus heyneanus*. *Tetrahedron*, **27,** 1013–1026.

————(1971*a*). Ishwaro, a new tetracyclic sesquiterpene alcohol from *Aristolochia indica* Linn. *Indian J. Chem.*, **9,** 1310.

Govindachari, T. R., Parthasarathy, P. C., and Desai, H. K. (1971*a*). Chemical investigation of *Ancistrocladus heyneanus* Wall : Part III. Further studies on Ancistrocladine. *Indian J. Chem.*, **9,** 931–935.

————(1971*b*). Ancistrocladinine, a minor alkaloid from *Ancistroc ladus heyneanus* Wall. *Indian J. Chem.*, **9,** 1421–1422.

————(1972). Chemical Investigation of *Ancistrocladus heyneanus* Wall. Part VI. Isolation and structure of Ancistrocladisine, a novel alkaloid. *Indian J. Chem.*, **10,** 1117–1119.

————(1973 *a*). Chemical investigations of *Ancistrocladus heyneanus* Wall. Ancistrocladicine, a new isoquinoline alkaloid. *Indian J. Chem.*, **11,** 1190–1191.

Govindachari, T. R., Parthasarathy, P. C., Desai, H. K., and Mohamed, P. A. (1973 *b*). 5BH, 7B, 10a–Selina-4 (14), 11-diene, a new sesquiterpene hydrocarbon from *Aristolochia indica Linn. Indian J. Chem.*, **11,** 971–973.

Govindachari, T. R., Parthasarathy, P. C., Desai, H. K., and Shanbhag, M. N. (1973 *c*). Structure of *Cryptocaryone. Tetrahedron,* **29,** 3091–3094.

Govindachari, T. R., Parthasarathy, P. C., Pai, B. R. and Kalyanaraman, P. S. (1968). Chemical investigation of *Andrographis serpyllifolia* : Isolation and structure of Serpyllin, a new flavone. *Tetrahedron,* **24,** 7027–7031.

Govindachari, T. R., Parthasarathy, P. C., Pai, B. R., and Subramaniam, P. S. (1965 *b*). Chemical investigation of *Andrographis wightiana* : Isolation and Structure of Wightin, a new flavone. *Tetrahedron,* **21,** 3237–3245.

————(1965 *c*). Chemical Examination of *Andrographis echioides*—I. Structure and synthesis of Echioidinin. *Tetrahedron,* **21,** 2633–2640.

————(1965 *d*). Chemical Examination of *Andrographis echioides*–II. Structure and synthesis of Echioidin. *Tetrahedron,* **21,** 3715–3720.

Govindachari, T. R., Parthasarathy, P. C., Rajagopalan, T. G. Desai, H. K., Ramachandran, K. S., and Eun Lee (*Unpublished work*).

Govindachari, T. R., Pillai, P. M., Nagarajan, K. and Viswanathan, N. (1965 *d*). Synthesis of 5– and 8– Methoxyobyrines. *Tetrahedron,* **21,** 2957–2960.

Govindachari, T. R., and Rajappa, S. (1961). Echitamine. *Tetrahedron,* **15,** 132–143.

Govindachari, T. R., Rajagopalan, T. G., and Viswanathan, N. (1974 *a*). Absolute Configuration of Tylophorine. *J. chem. Soc. Perkin I,* 1161–1165.

Govindachari, T. R., Ravindranath, K. R., and Viswanathan, N. (1974 *b*). Mappicine, a minor alkaloid from *Mappia foetida Miers. J. chem. Soc. Perkin I,* 1215–1217.

Govindachari, T. R., and Viswanathan, N. (1972). Alkaloids of *Mappia foetida. Phytochemistry,* **11,** 3529–3531.

Govindachari, T. R., Viswanathan, N., and Mohamed, P. A. (1971 *c*). Structure of Litsomentol, a new tetracyclic triterpene. *Tetrahedron,* **27,** 4991–5009.

Govindachari, T. R., Viswanathan, N., Pai, B. R., and Savitri, T. S. (1965*e*). Chemical Constituents of *Alstonia venenata* R. Br., *Tetrahedron,* **21,** 2951–2956.

Govindachari, T.R., Viswanathan, N., Radhakrishnan, J., Pai, B. R., Natarajan, S., and Subramaniam, P. S. (1973 *a*). Minor Alkaloids of *Tylophora asthmatica.* Revised structure of Tylophorinidine. *Tetrahedron,* **29,** 891–897.

Grant, I. G., Hamilton, J. A., Hemor, T. A., Hodges, R., McGeachin, S. G., Raphael, R. A., Monteath-Robertson, J., and Sim, G. A. (1961). The structure of Cedrelone. *Proc. chem. Soc.,* 444–445.

Hamilton J. A., Hamor, T. A., Monteath-Robertson, J., and Sim, G. A. (1961). The structure of Echitamine. *Proc. chem. Soc.,* 63.

Joshi, B. S., Kamat, V. N., Gawad, D. H., and Govindachari, T. R. (1972). Structure and synthesis of Heptaphylline. *Phytochemistry,* **11,** 2065–2071.

Joshi, B. S., Kamat, V. N., and Govindachari, T. R. (1967*a*). *Sesquiterpenes of Neolitsea zeylanica Merr.*—I. Isolation of some constituents. *Tetrahedron,* **21,** 261–265.

————(1967*b*). *Sesquiterpenes of Neolitsea zeylanica Merr.*–II. Structure of Neolinderane. *Tetrahedron,* **23,** 267–271.

————(1967*c*). *Sesquiterpenese of Neolitsea zeylanica Merr.*–III. Structure of Zeylanine, Zeylanicine and Zeylanidine. *Tetrahedron,* **23,** 273–277.

Joshi, B. S., Kamat, V. N., Govindachari, T. R., and Ganguly, A. K. (1969). Isolation and structure of Surangin-A and Surangin-B, two new coumarins from *Mammea longifolia (Wight) Planch and Triana. Tetrahedron,* **25,** 1453–1458.

Manohar, H., and Ramaseshan, S. (1963). The Absolute Configuration of Echitamine Iodide by the X-Ray Technique. *Proc. Indian Acad. Sci.,* A, **58,** 109–124.

Mulchandani, N. B., Iyer, S. S., and Badheka, L. P. (1969). Incorporation of Tyrosine-2-^{14}C into Tylophorine. *Phytochemistry*, **8**, 1931–1935.

————(1971). Incorporation of Phenylalanine-2-^{14}C into Tylophorine. *Phytochemistry*, **10**, 1047–1050.

————(1971 *a*). Structure of Tylophorinidine : A new potential antitumour alkaloid from *Tylophora asthmatica* plants. *Chemy. Ind.*, 505–506.

Rao, U. S. K., Manjunath, B. L., and Menon, K. N. (1935). Chemical Examination of the Roots of *Aristolochia indica* Linn. *J. Indian Chem. Soc.*, **12**, 476–485.

Rapoport, H., and Baldridge, H. D. (1951). The Carbon Skeleton of Carpaine. *J. Am. Chem. Soc.*, **73**, 343–346.

Shivpuri, D. N., Menon, M. P., and Prakash, D. (1969). A Gross-over Double-blind study on *Tylophora indica* in the treatment of asthma and allergic rhinitis. *J. Allergy*, **43**, 145–150.

Spiteller-Friedmann, M., and Spiteller, G. (1964). *Anwendung der Massenspektrometrie zur Struktur-aufkla-rung von Alkaloiden 5. Mitt. Monatsh.*, **95**, 1234–1241.

Wadhawan, V. K., Sikka, S. K., and Mulchandani, N. B. (1973). Minor alkaloids of *Tylophora Asthmatica* : X-ray Analysis of Tylophorinidine. *Tetrahedron Lett.*, 5091–5094.