Asima Chatterjee: A Unique Natural Products Chemist

Asish De

Asima Chatterjee, along with T R Seshadri[1], T R Govindachari[2] and K Venkataraman, is one of the best known Indian natural products chemists of the last century. She has made significant contributions to the chemistry of alkaloids, coumarins and other plant products. By her relentless research efforts, she was able to isolate a large number of natural products from many species of plants indigenous to the Indian subcontinent, unravel their structure by degradative, spectroscopic and synthetic procedures. In the process, she developed new synthetic methods, discovered mechanisms of reactions and brought to light other aspects of natural products that she studied, such as chemotaxonomy and their medicinal applications.

Asish De, Formerly Senior Professor at IACS, Kolkata, now teaches at NIPER, Kolkata. He is involved in teaching postgraduate students in a number of local universities. His research interests are primarily in the field of heterocyclic chemistry, especially sulfur heterocycles – synthesis, physicochemical studies and application of directed metalation, which also involve an interdisciplinary collaboration consisting of photo-induced electron transfer studies.

[1] *Resonance*, Vol.9, No.2, 2004.
[2] *Resonance*, Vol.13, No.6, 2008.

Keywords
Alkaloids, yobyrine, yohimbine, rauwolsine, crotocaudin, 3-indanone, coumarins, natural products

Introduction

India is rich in flora with medicinal properties and there is a long history of their use in folk medicine. The use of medicinal plants to treat diseases was institutionalized in India under the Ayurvedic system of treatment that is still in vogue today. This system received renewed attention with the advancement of chemical science, especially of a branch of organic chemistry, called natural products chemistry. For a long time, natural products chemists' research activity has been to painstakingly separate the chemical components of plants and other living organisms, including those of marine sources, followed by elucidation of their molecular structure. In the days when spectroscopic and other instrumental facilities were sparse, chemical degradation was the main tool available to derive these complex structures, which required not only sound chemical knowledge, but also good experimentation skills. The proof of the proposed structure of a molecule finally came from unambiguous total synthesis. A part of this research activity was to identify the 'active principles' that are responsible for the molecule's biological activities. Isolation

and purification of these 'active principles' was an onerous task because they are present in minute amounts. One of the prominent natural products chemists of India was Asima Chatterjee (1917–2006).

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Early Life and Family

Asima Chatterjee (née Mookerjee) was born on September 23, 1917, in Calcutta. She was the elder of the two children of Indra Narayan Mookerjee, a medical doctor, and Kamala Devi. Her brother, Sarashi Ranjan Mookerjee, later became a renowned surgeon and collaborated with his sister in her research on medicinal plants. Asima passed intermediate (science) examination from Bethune College and completed her graduation from Scottish Church College, Calcutta, with Chemistry Honours, receiving a number of medals in her undergraduate examinations. She obtained MSc degree from Calcutta University in 1940, winning a silver medal.

Asima married Baradananda Chatterjee in 1945. Baradananda Chatterjee was a physical and soil chemist who became well known in his field, and became a Fellow of the Indian National Science Academy. They had a daughter, Julie Banerjee, their only child, who became a professor of organic chemistry at Calcutta University. The immense contribution made by Asima Chatterjee to Indian science in general, and organic chemistry in particular, would have been impossible without the moral support she received from her husband. The broadmindedness and the progressive outlook of her husband in encouraging her – a young middle class Bengali woman – in pursuing her interests, was not common in the first half of the 20th century. Asima was, in a way, lucky to have had the right liberal environment in both her parents' and husbands' families which helped her achieve so much in chemistry research and carve out a special niche for herself in Indian science.

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Research Career

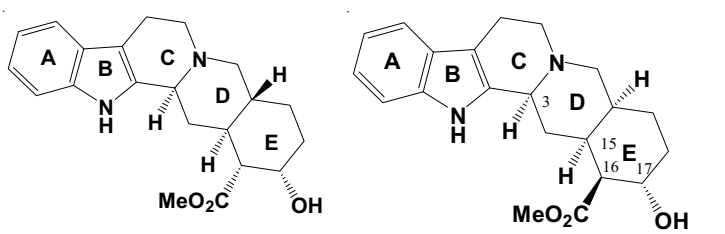
After obtaining the master's degree, Chatterjee started her

Asima's many-sided research activity led to a voluminous body of results.

research in 1940 under the guidance of Prafulla Kumar Bose at the University College of Science, and simultaneously started teaching at the Lady Brabourne College, Calcutta. She obtained DSc degree from the Calcutta University in 1944, and was immediately appointed there as an Honorary Lecturer in Chemistry. In 1947, she went on a study leave for three years, first to the United States and then to Europe. In the US, she worked with L M Parks at the University of Wisconsin and with L Zechmeister, a leading worker in the chemistry of plant pigments and chromatographic technique, at the California Institute of Technology. In Europe, she worked with the 1937 Chemistry Nobel Prize winner Paul Karrer at the University of Zurich on biologically active alkaloids. In 1954, she was appointed Reader in the Department of Chemistry, Calcutta University, and in 1962, she became the Khaira Professor, a Chair she held until her retirement in 1982. In 1972, the University Grants Commission sanctioned a Special Assistance Programme to the organic chemistry section of the Chemistry department of the university, which was recognized as the Centre of Advanced Studies in Natural Products in 1985. After her retirement as Khaira Professor, Chatterjee continued as the honorary Coordinator of that Centre till the last days of her life. She passed away in 2006.

In the days when Chatterjee began her research career, the instrumentation facilities available were sparse. But that did not deter her from taking up investigation of structures of complex molecules. Modern facilities like high resolution nuclear magnetic resonance (NMR) and mass spectrometry became available to her only in the later part of her career, which she utilized to the fullest extent. In addition to structural analysis, she carried out multistep total syntheses, mechanistic studies and testing of the active principles isolated from medicinal plants for their effectiveness as remedies against illnesses. This many-sided research activity led to a voluminous body of results. However, in this article, only a glimpse of it is discussed.

Chatterjee's work on natural products can be discussed under the following heads.



Alkaloids were investigated extensively by Asima for over four decades.

1. *Alkaloids*

Rauwolfia alkaloids, which occupy an important position among alkaloids, were investigated extensively by Chatterjee for over four decades. Rauwolscine, (a central nervous system stimulant, local anesthetic and aphrodisiac), isolated from *Rauwolfia canescens* was shown to have yohimbinoid structure (**1**) like the other *Rauwolfia* alkaloids, reserpine and deserpidine. Its pentacyclic structure was established by selenium dehydrogenation and other elaborate chemical transformations [1], and its relative and absolute configurations of the different stereogenic centers were determined to show rauwolscine as α-yohimbineline.

The structural elucidation involved establishing the location of the methoxycarbonyl and the secondary hydroxyl functions in the ring E by the following chemical transformations (*Scheme* 1).

Chatterjee isolated and determined the structures of several other alkaloids. Some of the important ones among them are flexicorine (**3**), a bis-indole alkaloid isolated from *Rauwolfia reflexa,* piperlongumine (**4**) and piperlonguminine (**5**) (both reported to have anticancer activity) isolated from *Piper longum,* aegeline (**6**), aegelenine and halopine (**7**) [2] isolated from *Aegle marmelos* (which yields edible fruits and contains coumarins along with alkaloids), and a new acridone alkaloid atalaphyllidine (**8**) isolated from *Atalantia monophylla.* Chatterjee extensively used UV, mass and NMR spectroscopic techniques, and chemical transformation studies to derive their structures. In several of these investigations, as in the case of **4** and **5**, she confirmed their structures by unambiguous synthesis.

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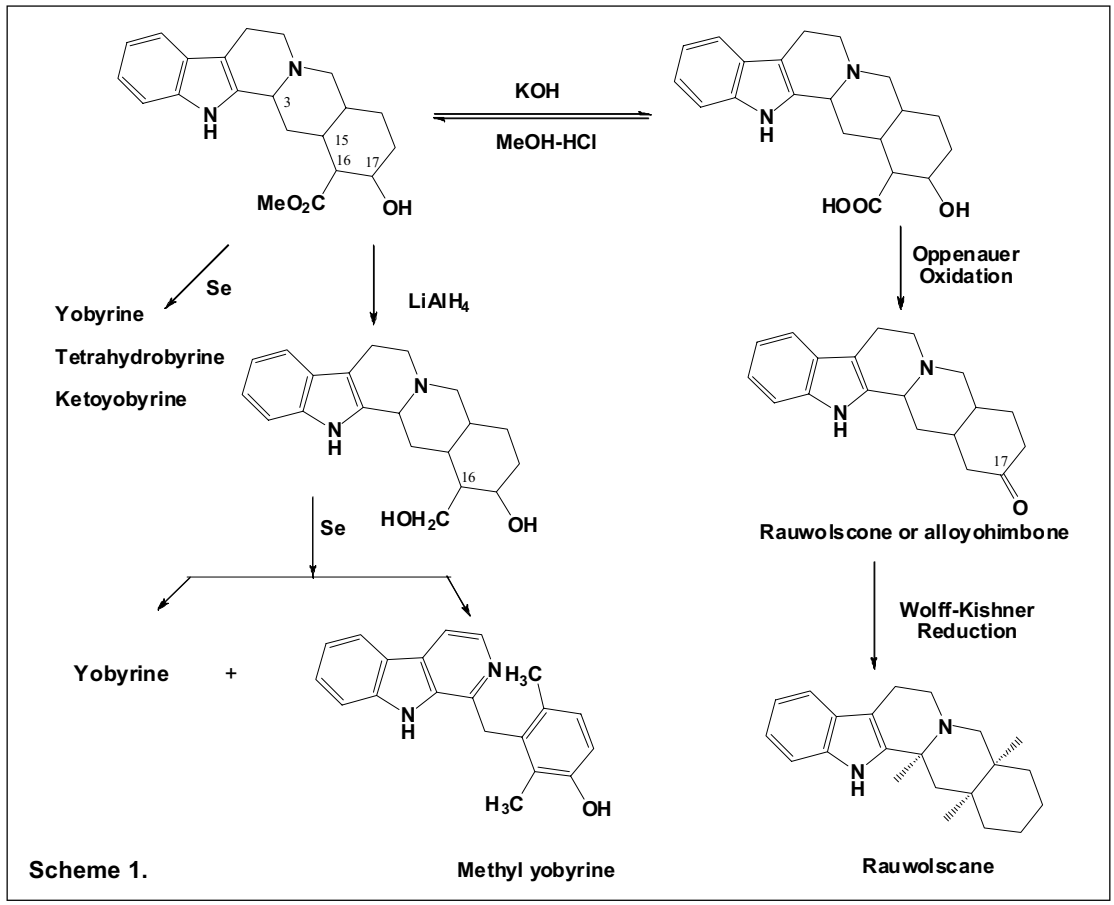
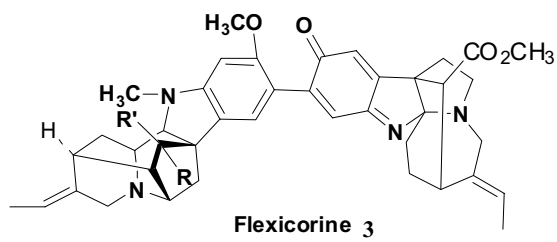
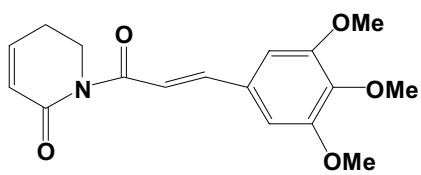


Scheme 1.

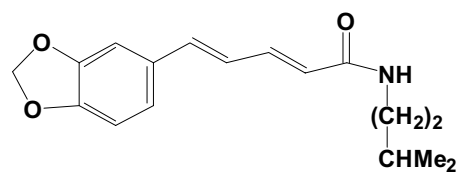


Flexicorine 3

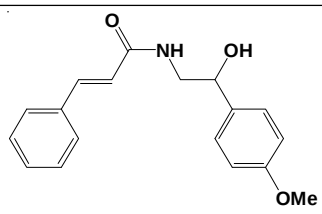
R = R' = O



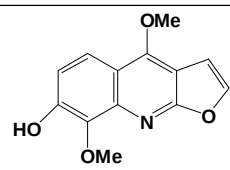
Piperlongumine 4



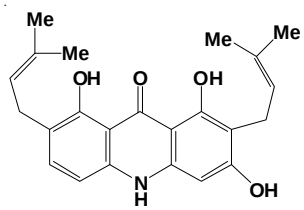
Piperlonguminine 5



Aegeline **6**



Halopine **7**



Atalaphyllidine **8**

Chatterjee's investigations on the alkaloids of *Rhazya stricta* have an important bearing on the biogenetic pattern observed in this species [3]. She has also reported about her investigations on monoterpene alkaloids [4], diterpene alkaloids [5] and steroidal alkaloids [6].

2. *Coumarins*

Coumarins received Chatterjee's attention early in her research career, which started with the elucidation of the structure of luvangetin isolated from *Luvanga scandens*. *Aegle marmelos* and *Prangos pabularia* are sources of coumarin derivatives as also alkaloids. The former, popularly known as Bael, yields edible fruits, and is the only member of the monotypic genus *Aegle*, a species of tree native to India and the countries of South East Asia. Its fruits and bark are effective against gastrointestinal disorders and the bactericidal properties are attributed to the essential oils present in it. *Prangos pabularia* is a perennial herb widely distributed in the area ranging from Russia to Iran. In the Indian subcontinent, it is found in the Northern mountains of the Himalayas and Baluchistan. The plant's use in folk medicine and the allelopathic[1] properties of the essential oil in its leaves have been reported.

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[1] Allelopathy is a plant survival strategy in which such plants exude certain chemical compounds in minute quantities that act against the growth of other plants around themselves, so that they do not face the threat of competition for nutrients.

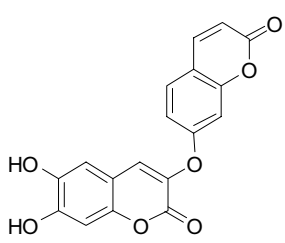
Chatterjee established the structure of marmesin (**9**), the most important one of the seven coumarins isolated from *Aegle marmelos*, by the classical chemical degradation process [7]. It is the biogenetic precursor of other linear furocoumarins. The structure of this compound has recently been investiaged by crystallographic studies [8].

The bis-coumarin edgeworthin (**10**) consisting of two coumarin units and a dibenzocoumarin, trimethylellagic acid (**11**) were isolated respectively from *Edgeworthia gardneri* and *Euphorbia tirucalli*.

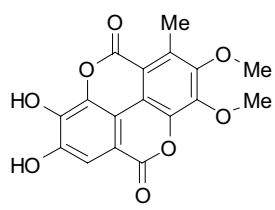
Among the furanocoumarins isolated from *Prangos pabularia*, mention may be made of prangolarine, pabularinone and pabulenol (**13**) [9]. Pabulenol's simultaneous occurrence with several other furanocoumarins like isoimperatorin, oxypeucedanin and isooxypeucedanin is considered to support the hypothesis advanced by Hendrickson and Richards for the biogenesis of isoprenoid side chains [10].

3. *Terpenoids*

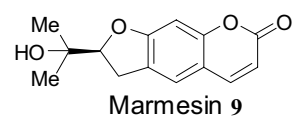
Chatterjee investigated the medicinal plants *Leuconatis eugenifolia*, *Dillenia indica*, *Callicarpa polystachia*, *Alstonia neriifolia* and *Ferula assafoetida*, which were sources of several triterpenes, diterpenes, diterpene alkaloids and sesquiterpenoid coumarins. The structures were established from chemical degradation as well as spectroscopic studies.



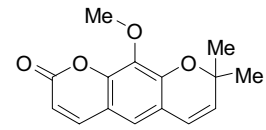
Edgeworthin **10**



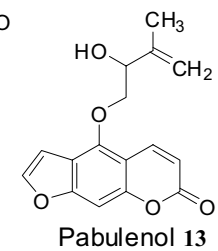
Trimethylellagic acid **11**



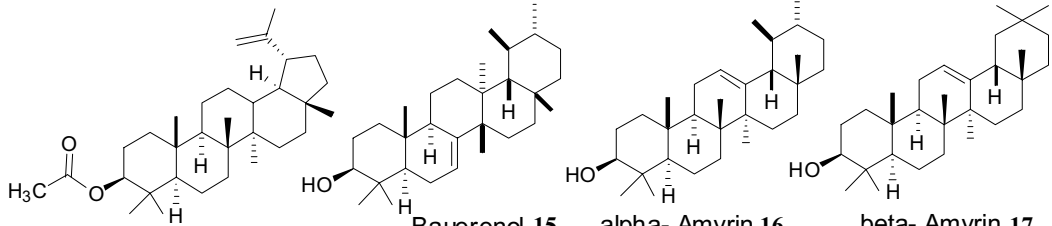
Marmesin **9**



Luvangetin **12**



Pabulenol **13**



Lupenyl Acetate **14** Bauerenol **15** alpha- Amyrin **16** beta- Amyrin **17**

Chatterjee *et al* isolated lupenyl acetate (**14**) from the leaves of *Leuconotis eugenifolia* and an apparently new triterpene alcohol which was named as leuconol, but later found that leuconol is probably a mixture consisting of bauerenol (**15**), α- and β-amyrin (**16** and **17**).

Chatterjee's chemical investigation of a good number of plants of the Indian subcontinent and Southeast Asia, which involved laborious and in those days challenging task of isolation and identification, yielded rich dividend in the area of terpenes. She was able to establish the presence of many terpenes, some of which were known and some others new, in a number of plant species, particularly in those native to the Indian subcontinent. For example, betulin and betulinic acid from *Dillenia indica* (elephant apple, whose fruit pulp is bitter-sour and used in preparing curries in certain parts of India. The fruits are the main source of food for wild animals like elephants, monkeys, deer etc.), lupeol and amyrin from *Alstonia neriifolia*, and calliterpenone (shown to be 7-keto-β-amyrene) from *Xanthoxylum rhetsa.*

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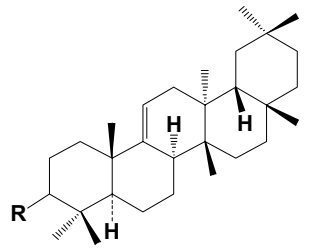
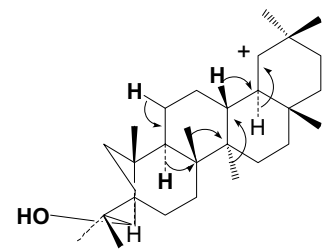
Chatterjee studied the *Aphanamaxis polystachia* species belonging to Meliaceae family. The presence of the hemiacetal function in apharamaxin isolated from this species led her to propose the biogenetic origin of the compound. She isolated and identified the terpene alcohol, walsurenol (**18**), from *Walsura tabulana* which also belongs to the Meliaceae family. From these results, she hypothesized that apharamaxin and walsurenol are biogenetically derived from a common ion (**19**). For deducing the structures of these compounds, Chatterjee used oxidation and



Walsurenol 18

R=(H, ---OH)

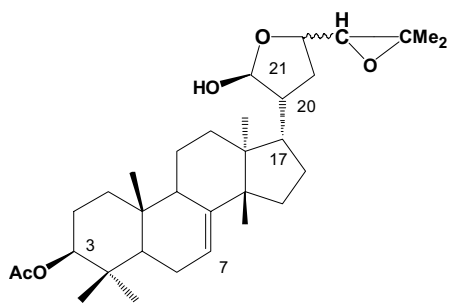


Common ion 19

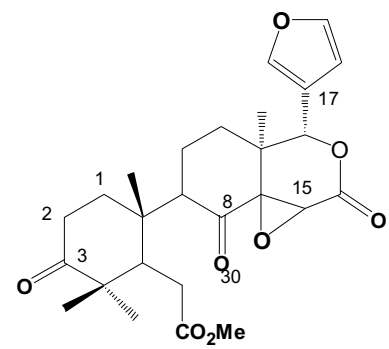
reduction reactions and NMR spectral data including results obtained from using shift reagents, NOE and deuterium exchange procedures.

Other examples of the combined application of chemical and spectroscopic methods in the elucidation of the structures are the triterpene alcohols aphanamixin (**20**), aphanamixinin (**21**) and aphananin, all isolated from *Aphanamixis polystachia*.

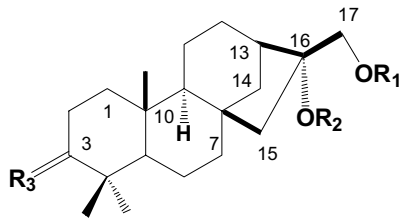
Using high-resolution NMR data, Chatterjee elucidated the structures of the two diterpenoids, calliterpenone (**22**) and calliterpenone monoacetate (**23**), which were isolated from *Callicarpa macrophylla.*



Aphanamaxin 20



Aphanamaxinin 21



Calliterpenone $R_1 = R_2 = H$, $R_3 = 0$ – (22)

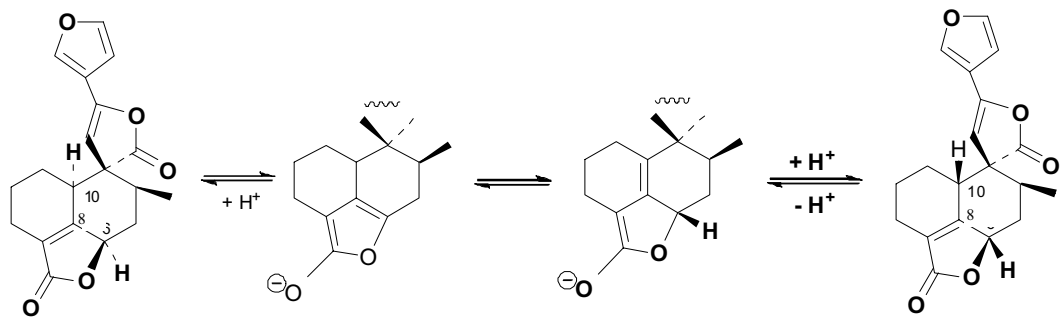
Calliterphenone monoacetate $R_1 = Ac$, $R_2 = H$, $R_3 = 0$ – (23)

Likewise, using NMR data, she elucidated the structure and stereochemistry of the two furanoid diterpenes, crotocaudin (**24**) and isocrotocaudin (**25**) isolated from *Croton caudatus.*

Crotocaudin could be converted to isocrotocaudin via $NaBH_4$ reduction in methanol. The conversion was considered to take place through the intermediacy of an enolate anion and it was concluded that the methyl group of isocrotocaudin has a β-orientation (*Scheme* 2).

Much later, a correction was made in the stereochemistry of H-8 based on the conversion of montanin A with known H-8 stereochemistry to isocrotocaudin via opening of the C-20, C-12 γ-lactone of the former followed by relactonisation (*Scheme* 3) [12]. Since the stereochemistry of the H-8 was not disturbed during this process, it was inferred that H-8 in isocrotocaudin has

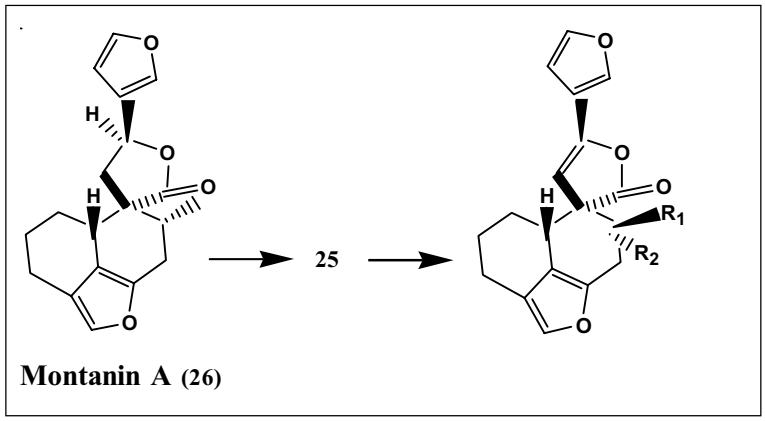
Scheme 2.



Crotocaudin 24

Isocrotocaudin 25

Scheme 3.



Montanin A (26)

8-(*R*) configuration as in montanin A (**26**) rather than 8-(*S*) configuration as suggested earlier.

4. *Synthesis and Mechanistic Studies*

Chatterjee skillfully used the 6-membered lactones obtained by Bayer–Villiger oxidation of 1- and 2-indanone derivatives as key intermediates in elegant and practical multistep syntheses of several natural products.

Thus, 3-isochromanone and its derivatives, obtained by Bayer–Villiger oxidation were used in the syntheses of a number of alkaloids. 2-indanone, the precursor of 3-isochromanone, was expediently synthesized via diazoketone cyclization with TFA. The isochromanone constituted the non-nitrogenous part of several alkaloids synthesized by Chatterjee. An example can be found in the total synthesis of (±) Rauwolscine (**2**) (*Scheme* 4), an important rauwolfia alkaloid [13]. The nitrogenous part of the alkaloid was incorporated by the reaction of isochromanone with tryptamine.

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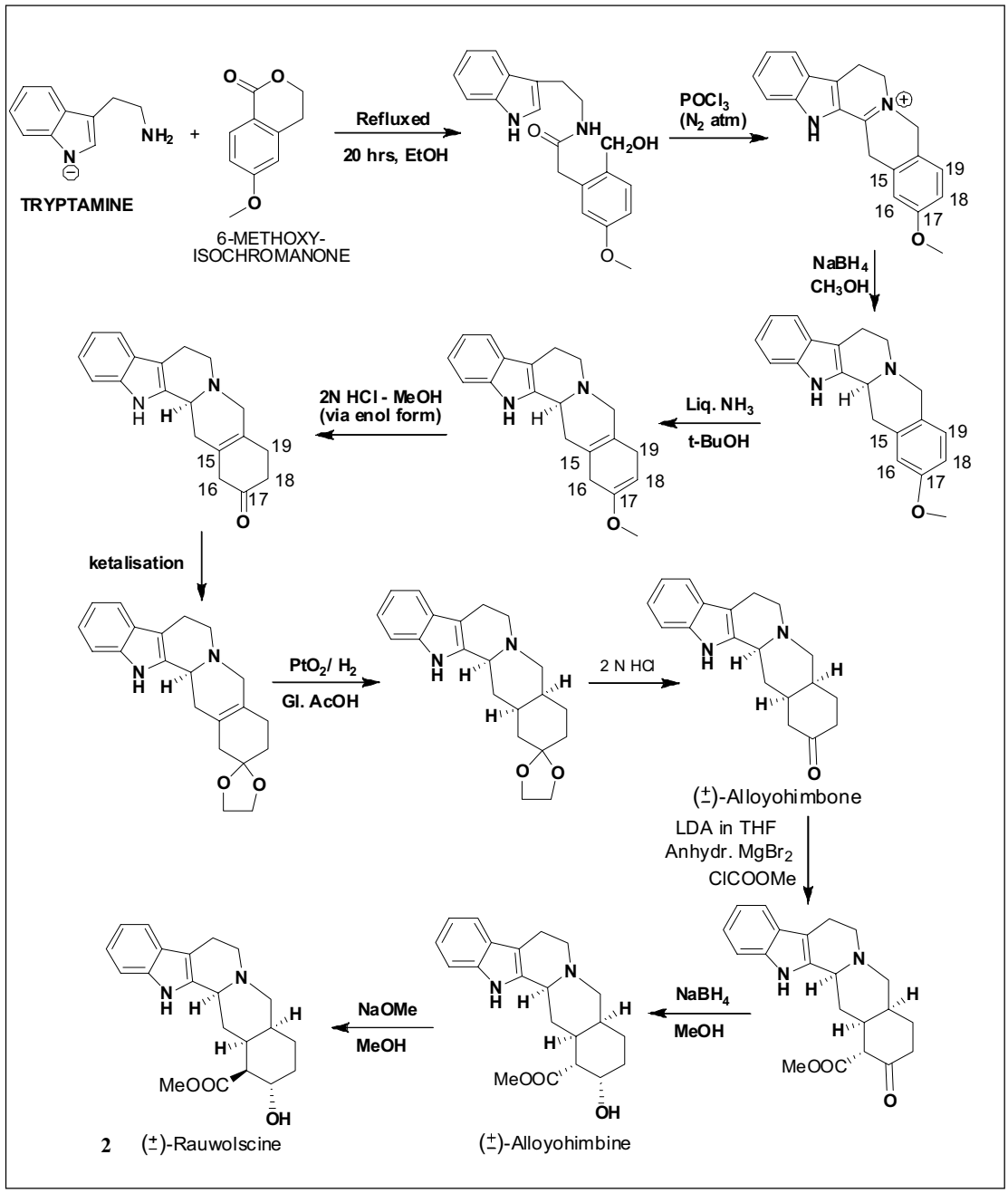
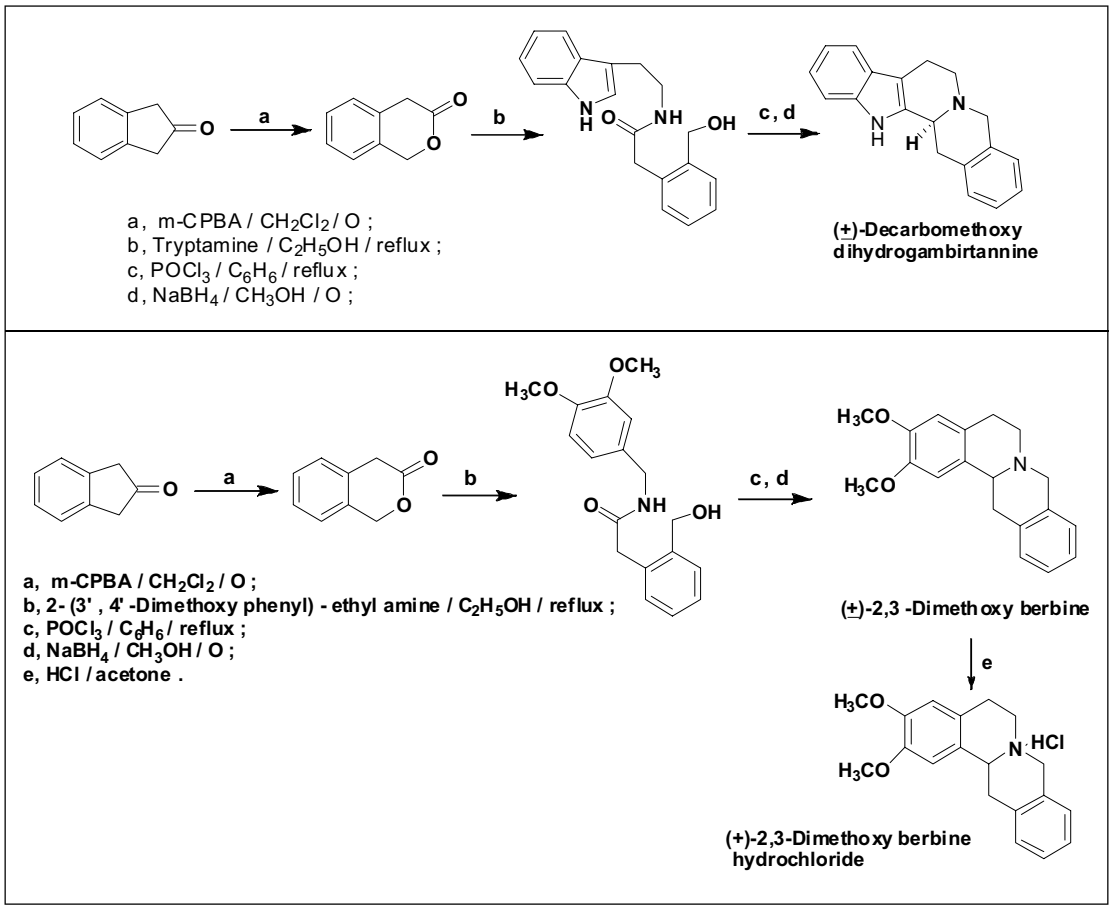
Isochromanone also served as a key intermediate in the synthesis of three alkaloids having protoberberine skeleton, viz., dihydrogambirtannine (*Scheme* 5), 2,3-dimethoxyberbine (*Scheme* 6) and norcoralydine.

Chatterjee reported a number of synthetic and mechanistic studies carried out on indole derivatives. The Duff reaction on indole



Scheme 4. Synthesis of ± rauwolscine.

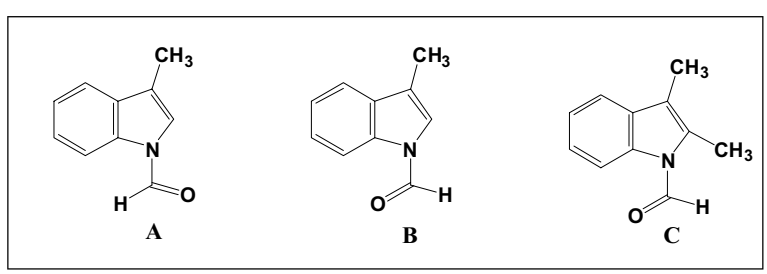
afforded the 3-carboxaldehyde. Vilsmeier–Haack formylation of 3-methylindole resulted in the formylation on nitrogen as well as in the 2-position, accompanied by the ring opening. Under the same reaction conditions, 2,3-dimethylindole exclusively afforded

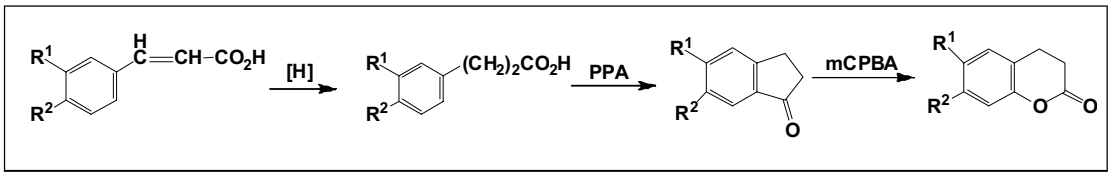


Scheme 5 (top). Synthesis of ± decarbomethoxy dihydro-gambirtannine.

Scheme 6 (bottom). Synthesis of ± 2, 3 dimethoxyberbine hydrochloride.

the *N*-formyl derivative. NMR studies revealed that the aldehyde function in 3-methyl indole-1-carboxaldehyde existed in two conformers (**A**) and (**B**) but only one conformer (**C**) could be detected in 2,3-dimethylindole-1-carboxaldehyde.





Scheme 7. Bayer–Villiger oxidation.

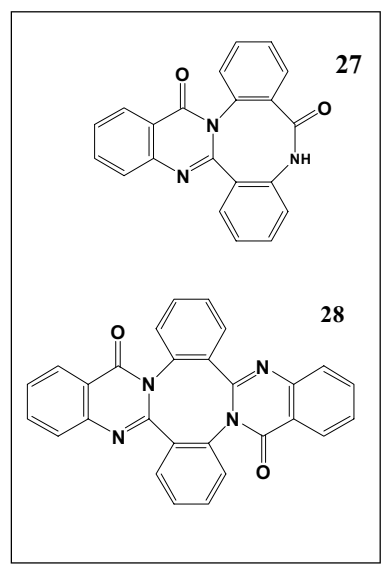
Metal hydride reduction of these *N*-formyl derivatives resulted in the removal of the aldehyde function while reduction with diborane afforded dimeric products whose structures were established from their mass spectral fragmentation patterns [14]. A series of in-depth studies were carried out on electrophilic substitution on indole [15].

A novel synthesis of coumarins from cinnamic acids was reported by Chatterjee. The key step is the Bayer–Villiger oxidation of the intermediate 1-indanone with *m*-chloroperbenzoic acid (*Scheme* 7).

Chatterjee studied the mechanisms of several unusual reactions of naturally occurring coumarins and furanocoumarins [16,17]

During the attempted synthesis of deoxyvascinone two new compounds (**27** and **28**) were isolated, the major one, **27**, resulting from thermal trimerization of anthranilic acid, which on further heating with anthranilic acid could be converted to **28**.

5. *Medicinal Applications of Natural Products*



Therapeutic effects of alkaloids derived from various *Rauwolfia* species were reported by Chatterjee. Chatterjee and Mukherjee made thorough investigations on two species of water fern *Marsilea minuta* and *Marsilea rajasthanensis* [18]. Marsilin, the active principle of these water ferns showed pronounced therapeutic effect in the treatment of epilepsy.

The antifertility effect of the leaves of commonly known 'Piper betel' (betel leaves) was investigated by Chatterjee and Mukherjee [19]. Chemical and pharmacological properties of the herb 'Brahmi' used in folk medicine as anxiolytic, for memory enhancement and cognitive improvement were

Chatterjee also carried out investigations on chemotaxonomy.

investigated by Chatterjee and Mukherjee [20].

In combination with *Nardostachys jatamansi*, marsilin is used as a rehabilitation drug under the name Ayush 56. Another drug, Ayush 64 has been reported by Chatterjee to possess antimalarial properties. Know-how for the manufacture of both these drugs has been handed over to the National Development Council, Government of India.

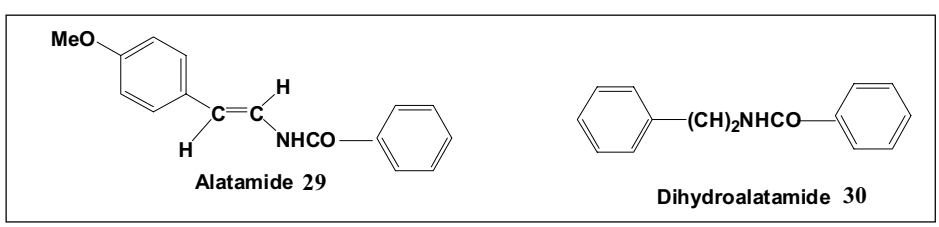
The glycoside 'neridin', isolated from *Nerium indicum* has been shown to provide nonspecific resistance to diseases.

6. *Chemotaxonomic Studies*

Chatterjee also carried out investigations on chemotaxonomy. In connection with the studies on chemotaxonomy of Rutaceae, Chatterjee isolated two secondary amides from *Plieospermium alutum*, viz., N-(*E*)-(*p*-methoxystyryl)benzamide, which was named alatamide (**29**) and N-benzoyltyramine methyl ether (dihydroalatamide) (**30**).

Biogenetically, alatamide may be derived from tembamide, another alkaloid belonging to the Rutacae family. Since the crude extract of the plant did not show the presence of tembamide, it is logically concluded that alatamide is not an artefact.

Asima Chatterjee's scientific contribution is many times more than what is presented above, and what is reported here is only a glimpse of her work in the major areas of her interest. However, her contributions in the many other areas which have been left out are no less important in terms of her scientific ability and to the field of organic chemistry in general and natural products in particular.



Alatamide **29** Dihydroalatamide **30**

Student Guidance and Publications

Asima Chatterjee was an inspiring and loving teacher who firmly believed that the university system is the harbinger of academic excellence. She trained a good number of students, both at undergraduate and graduate level. She supervised 59 PhD and 3 DSc students and published 328 research papers and a number of review articles. She edited six volumes of the revised edition of *Bharater Banousadhi*, a treatise in Bengali that deals with Indian medicinal plants and another six volumes of *The Treatise on Indian Medicinal Plants*, her magnum opus, published by the National Institute of Science Communication, CSIR, New Delhi. Apart from publishing the results of her research, she is credited with establishing a school of Natural Product Chemistry in the country.

Asima Chatterjee was an inspiring and loving teacher who firmly believed that the university system is the harbinger of academic excellence.

Awards, Honors and Recognition

Asima Chatterjee's contribution to scientific research was well recognized by several awards and honours. She received the Shanti Swarup Bhatnagar Award and was elected Fellow of both, the Indian National Science Academy and the Indian Academy of Sciences. She was a nominated member of the Upper House of Parliament (Rajya Sabha) and served as General President of the Indian Science Congress. She played a significant role in the formation of science education policy in our country. In sum, Asima Chatterjee was a unique scientific personality and an excellent educationist.

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