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TIRUVENKATAPURAM RAJENDRA SESHADRI SEVENTIETH BIRTHDAY COMMEMORATION MEDAL LECTURE–1979

REWARDS OF NATURAL PRODUCTS CHEMISTRY*

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I feel honoured that I have been selected by the Indian National Science Academy for delivering the Professor T R Seshadri 70th Birthday Commemoration Lecture for the year 1979.

Late Professor T R Seshadri was one of our most distinguished scientists. He was a great teacher and a researcher and inspired a generation by his dedication to science. He occupied many positions of significance, including the Presidentship of the Indian National Science Academy and was recognised nationally and internationally for his outstanding contributions. He was a Fellow of the Royal Society. The present speaker had the opportunity and privilege to intimately know him and also to accompany him as the member of several delegations overseas. Professor Seshadri has done more for us than we have done for him. It is a matter of regret that a man of his distinction, who had contributed so much to the growth of Indian science, had to spend the last few years of his life in great financial difficulties. It should not have been so.

I have selected the title of my talk as "Rewards of Natural Products Chemistry." This is an area of Chemistry in which the Indian chemists have made significant contributions and of them, Professor T R Seshadri is possibily the most distinguished. It will be, therefore, in the fitness of things, if a topic in this area is selected when we are trying to remember the contributions of this illustrious scientist.

The present speaker, along with his other activities, has taken a deep interest and devoted more than three decades on the study of the chemistry of natural products isolated from Indian sources. India, endowed, as it is, with widely different climatic conditions obtaining in different parts, is very rich in its diversified flora and fauna. These offer wonderful possibilities and opportunities to chemists interested in the chemistry of natural products.

While studying the chemistry of natural products, the earlier chemists, for obvious reasons, paid more attention to compounds which were crystalline in

*Updated version of the lecture delivered in the year 1980. The typescript was communicated by the author on June 25, 1986.

nature. These could be easily isolated and often formed the major bulk of an extractive. In such investigations, some of the constituents, which were present in comparatively minor proportions, were often lost in the mother liquors. However, with the newer techniques of extraction and isolation, which include chromatography in its different facets, counter current distribution, high pressure liquid column chromatography, etc., it is now possible to isolate almost all the constituents present in an extractive, including those occurring in micro and submicro quantities. We now know that plant extractives are much more complex than previously considered to be. It is not unusual that some of the extractives may contain over hundred constituents, many of which are closely related.

In recent years, the introduction of instrumental practices has brought about a revolution in our approaches to structure determination for which we previously had to depend primarily on degradative and synthetic approaches. The traditional methodologies are, no doubt, still very important, but, perforce, had to yield some ground to the newer techniques.

During the last forty years or so, we have also acquired some understanding about the genesis of natural products in plants and animals. This knowledge has often led to meaningful decisions in structure determination *via* correlation of the constituents present in the same source. All these newer developments have made the life of a scientist difficult, but, at the same time, more challenging.

It is amazing that, while preparing a simple compound such as acetanilide, we require fairly drastic conditions in terms of temperature and *p*H. Most of the plant and animal products are formed at the body temperature and often at the neutral *p*H conditions, from easily accessible and simple fundamental units. It is more amazing that, even in compounds having multiple assymetric centres, the required stereochemistry and optical purity are obtained and that mistakes are rarely committed by nature in executing such operations. If these points are kept in view while examining natural products, the exercise becomes very rewarding. In the present lecture some of these rewarding results are being presented.

In the course of our work on natural products, we examined only about 20 plants. The number of compounds isolated from these sources would exceed several hundreds. Of them over 100 are new compounds, the structures and stereochemistry of which, in most of the cases, have been elucidated by the applications of chemical reactions and spectral techniques. The separation of the constituents was achieved essentially by a combination of several practices in which chromatography in its different forms played the predominant part.

In the biogenesis of terpenes, geranyl and farnesyl pyrophosphates play crucial roles. They give rise to series of terpenoids of different structural types. Of the sesquiterpenes, which form an interesting and engaging group of natural products, over 70 structural types are now known. They belong to the acyclic, mono-, bi-, tri- and tetracyclic types without or with oxygen functions at different stages of oxidation. It is known, but does not seem to have been well appreciated, that the monocyclic compounds play a very crucial role in the biosynthesis of other

terpenoids. Many of these monocyclic compounds are subtle, thermolabile, photosensitive, autooxidisable, labile towards acid and alkali and may undergo changes under unwarranted conditions. Some of these are sensitive, so much so, that unless careful conditions are observed during their isolation, they might be lost due to polymerisation, denaturing, rearrangement and other changes, and one might be led to believe that they did not exist in the plants at all. However, if the method of isolation and the techniques employed for the separation of the constituents are adequately mild, then, it becomes possible to isolate and characterise some of these labile but crucial compounds. Keeping these points in view, we had carried out investigation on some well-known Indian plants which have been previously investigated by others. Two of these plants belong to the 'Compositae' family. The plant parts investigated are the roots of *Saussurea lappa* Clerk (costus root) and that of *Innula racemosa.*

'Compositae' plants are known to contain sesquiterpene lactones, several hundreds of which have been isolated in recent years from these plants and characterised structurally and stereochemically.[1,3] Compositae plants are also known to contain acetylenic compounds of unstable and often unusually complex nature and over 1500 such compounds have been recorded and their structures decided.[4]

Extraction of costus roots, with low boiling petroleum (40–60 °C) concentration, stagewise cooling of the extract, and chromatography of the portions on alumina, silica gel, ensuring that at no stage the temperature exceeded 40 ± 2 °C, led to the isolation of a series of compounds.[5,8] The majority of the isolates were terpenoids, some of which are shown in Chart-I. These are constunolide (1), *dihydro* costunolide (2), *dehydro* costus lactone (3), *dihydro-dehydro* costus lactone (4), *Saussurea* lactone (5), costol (6), and costic acid (7). There were many other constituents which occur in minor proportions including α and β-ionones (Chart-I).[9-11]

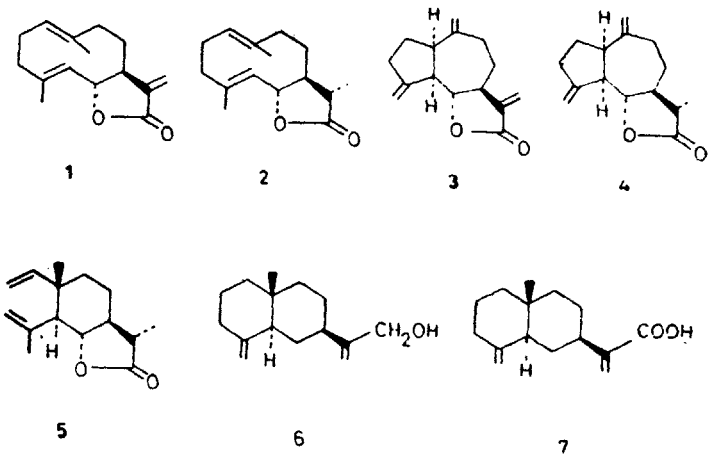


CHART I

Constunolide is one of those subtle compounds which undergo changes easily. In the presence of traces of acids it cyclises to β-*cyclo* costunolide (8) and α-*cyclo* costunolide (9). Similarly, *dihydro* costunolide, which can be obtained by controlled hydrogenation of costunolide, (1), in the presence of Palladium catalyst or by reduction with metal hydrides, on cyclisation gives the corresponding *dihydro* lactones, *dihydo* β-*cyclo* costunolide (10) and *dihydro* α-*cyclo* costunolide (11). All these cyclic loctones co-occur along with the monocyclic lactones as minor constituents (Chart-II).

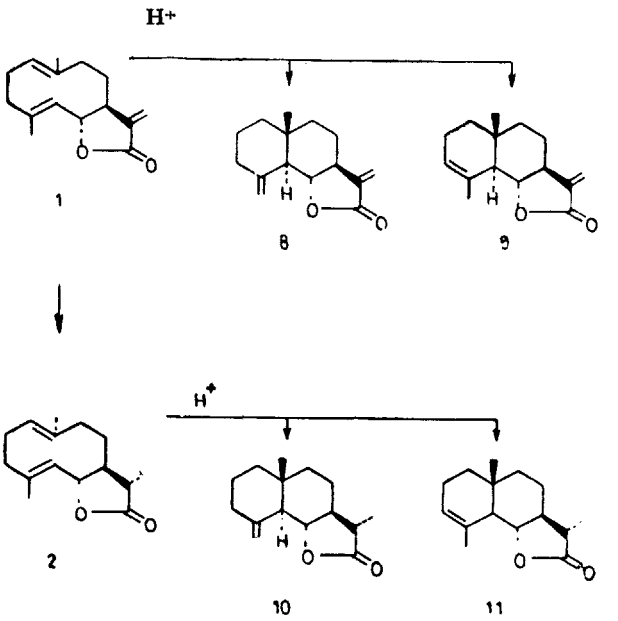


CHART II

Saussurea lactone (5), which is an elemenic compound, is closely related to elemol (14) to which it can be correlated synthetically by a series of reactions as shown in Chart-III and Chart IV.[12,13] It is, however. not a natural product and is derived *via* Cope rearrangement from *dihydro* costunolide under thermal conditions.

The structure of *Saussurea* lactone was decided by converting it to santanolide (13), obtained *via* cyclisation in the presence of acid to (10,11) followed by hydrogenation. It can also be synthesised from santonin (12), the well-known anthelmintic, which occurs in a 'Compositae' plant. This conversion confirms both the structure and absolute configuration of *Saussurea* lactone.

In the light of our knowledge of the structure of saussurea lactone and its genesis *via* pyrolytic Cope rearrangement of *dihydro* costunolide, it is reasonable to assume that the crystalline sesquiterpene alcohol, elemol (14), need not necessarily be a natural product, and could have been derived from a cyclic alcohol (21), which has been actually isolated in recent years, and have been shown to be converted to elemol by thermolytic Cope rearrangement.[14]

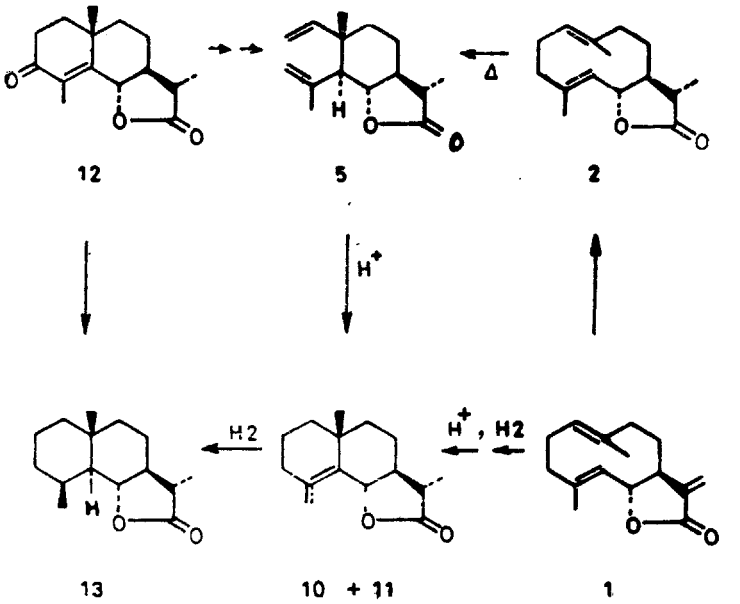
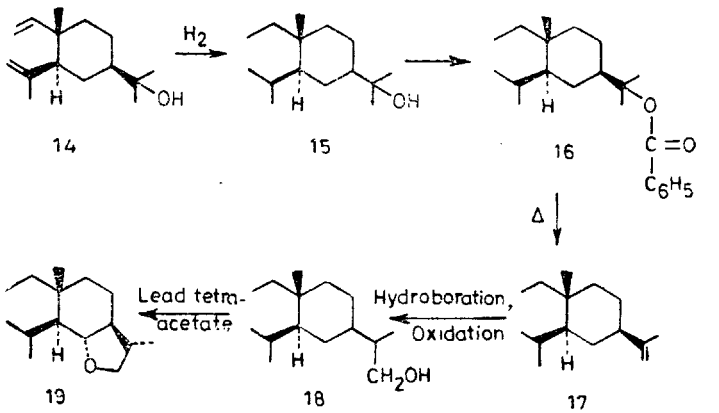


CHART III



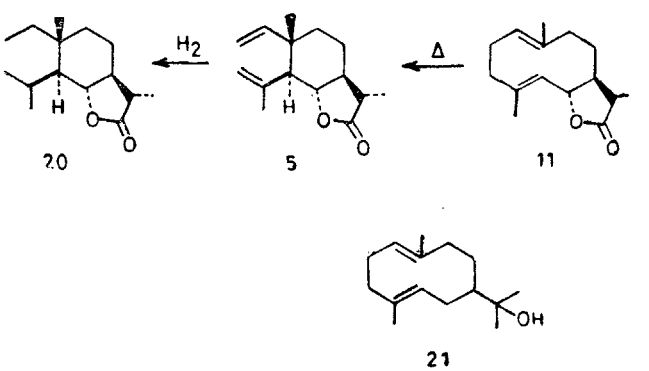


CHART IV

Though elemol had been known for a long time and its structure adequately established through degradative experiments, its absolute stereochemistry remained unestablished till it was decided by us by its actual conversion to *tetrahydro* Saussurea lactone. It will thus be clear, that costunolide and *dihydro* costunolide proved to be convenient compounds for solving several structural and stereochemical issues in terpene chemistry. A few other problems of structure and stereochemistry could also be sorted out with the help of these two lactones.

Thus, β-*cyclo dihydro* costunolide (10), by controlled reaction with LAH, followed by Wolf-Kishnner reaction yielded (+) junenol (23), which had been previously isolated by Sorm from the oil of juniper berry. The structure of this compound had been deciphered by him, but the stereochemistry remained undecided. (+) Junenol of Sorm proved to be an optical antipode of (—) junenol (26), obtained by us in micro quantities from North Indian *Vetiver* oil. We were able to decide the structure of the latter through our initial experiments, but could determine its stereochemistry only through the series of reaction connected with the conversion of *cyclo* costunolide and the corresponding *dihydro*-derivarive to (+) junenol and (+) *dihydro* junenol (25). The results are recorded in Chart V.

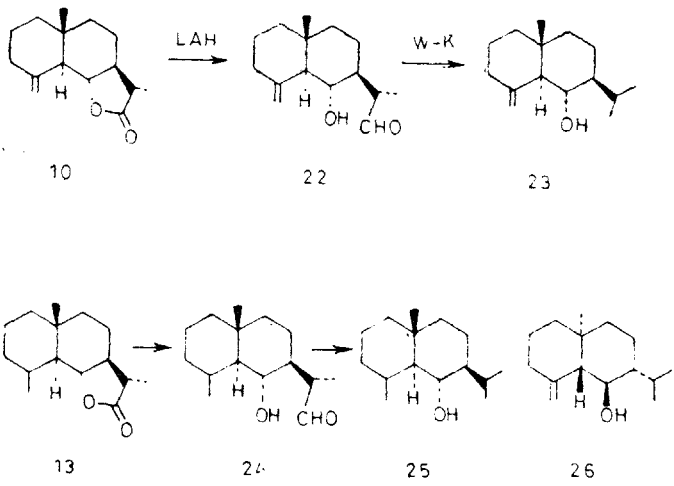


CHART V

By two other sets of experiments constunolide and *dihydro* costunolide could be correlated/converted to parthenolide derivatives (28) and santamarin (29), thus deciding the structure and stereochemistry of these compounds as shown in Chart-VI.[16,17]

It was also possible to determine the absolute stereochemistry of the C_{11} methyl group in santonin, with the help of costunolide. The stereochemistry of this methyl group had been a vexed problem which eluded decision even though several

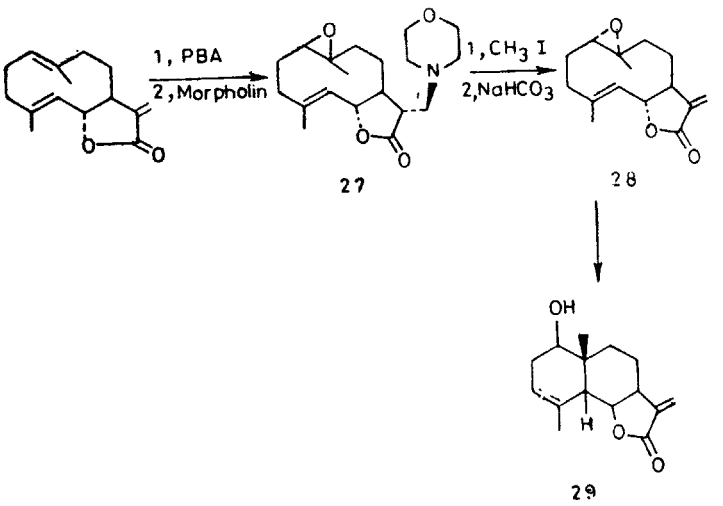


CHART VI

investigators were involved in this exercise. Eventually, solution was found from X-ray crystallography of a santonin derivative. A dependable degradative proof could be found from our experiments.[18]

Many of the lactones about which we have discussed contain an α-methylene–γ-lactone moiety. Such a system easily adds ammonia or any amine containing an available hydrogen atom, yielding highly crystalline adducts. By taking advantage of this, the conjugated lactones could be conveniently separated from the non-conjugated lactones. The amine adducts were stable and could be preserved indefinitely and from which *via* treatment with methyl iodide, followed by further treatement with mild alkali, the parent lactones could be regenerated in quantitative yield.[19] This technique made it possible for us to synthesise many unusual lactones which otherwise were difficult to obtain. It was also extremely helpful in the separation of complex mixture of lactones.

An unexpected finding was that costunolide or *dihydro* costunolide on treatment with selenium dioxide underwent oxidation on the C^{10} methyl group with conversion of the *trans* double bond to *cis*, yielding melampolides, a group of sesquiterpenoids which have been isolated only in recent years (Chart-VII).[20]

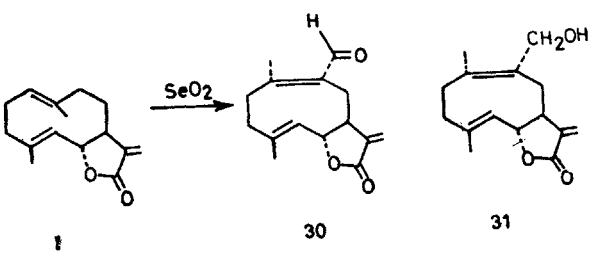
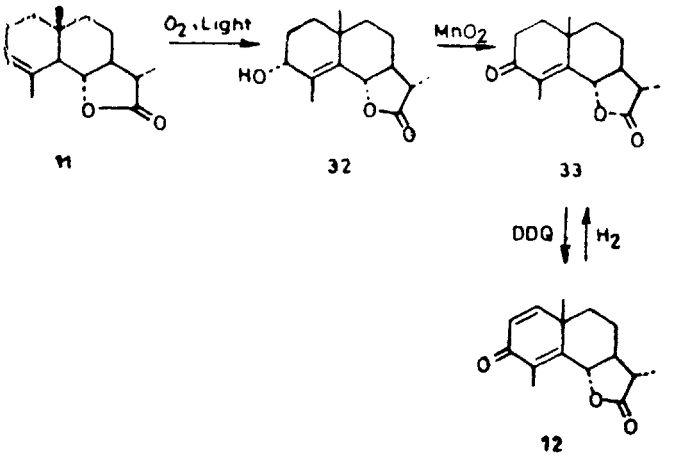


CHART VII

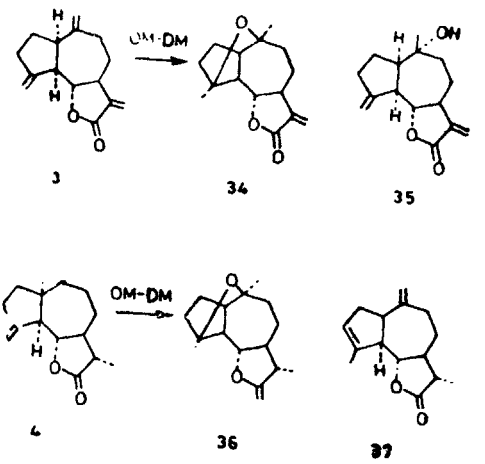
Another very fascinating experiment was the conversion of costunolide to santonin *via* photo-oxygenation and other steps.[21] Such a possibility was postulated by Professor D H R Barton and was demonstrated by the set of experiments carried out by us. Costunolide thus proved to be a very convenient compound and is possibly the precursor of many sesquiterpene lactones (Chart-VIII).



31 32 33 12

CHART VIII

Dehydro costus lactone (3) also proved to be an interesting compound and could be conveniently converted through oxymercuration-demercuration to several interesting naturally occurring oxygenated sesquiterpene lactones (34,35,36,37).[22] Similar products could also be obtained from costunolide and *dihydro* costunolide (Chart IX).

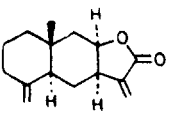


3 34 35

4 36 37

CHART IX

The other compositae plant, *Innula racemosa*, examined by us yielded several lactones of the alantolide series (38–43).[23,24] Of these, the monocyclic lactone, inunolide (42) is the linear equivalent of costunolide. As against the *trans* lactonic structure present in the costunolide derivatives, the inunolides contained *cisoid* structure.[25] Interesting transformations on these compounds were also carried out (Chart-X).



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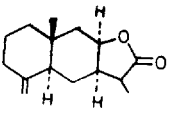

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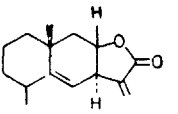

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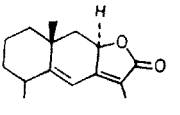

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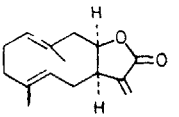

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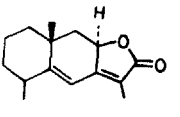

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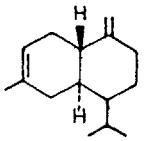
CHART X

While carefully studying the spectral characteristics of the lactones, it was found possible to distinguish between the *cis* and the *trans* lactones by examining their infrared spectra alone.

We also obtained unexpected but extremely rewarding results from our investigations on Indian *vetiver* oil.[26,29] For the first time, we isolated a family of antipodal sesquiterpenoids from the oil and characterised them in terms of their structure and stereochemistry. Indian *vetiver* oil seems to be a storehouse of terpenoids.[31–32] The total number of constituents in it far exceeded one hundred. Some of these (—) Y_2-cadinene (44), (—) *Y*-cadinene (45), crystalline alcohol, khusol (46), Khusinol (47), *epi*-khusinol (48), khusinol oxide (49), Khusilal (50), Khusilal acid (52), *laevo* junenol (26) (Chart XI).

We also examined the oils and the extractives of the infected and uninfected agarwood (*Aqualaria agalocha*), which led to the isolation of several interesting



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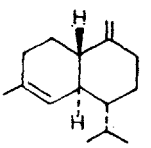

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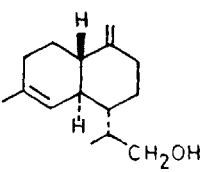

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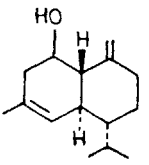

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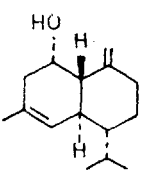

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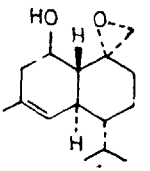

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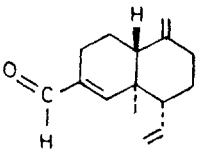

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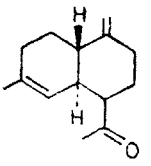

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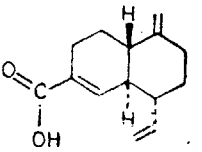

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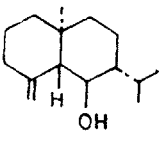

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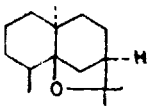
CHART XI

furanoid sesquiterpenes. These are α-agarofuran (53), β-agarofuran (54), *dihydro* agarofuran (55), hydroxyagarofurons (56,57), *nor*-ketoagarofuran (58) (Chart-XII).

A rare spiroterpenoid, agarospirol (59), was also isolated from agarood oil.[33'35] A few other important spiroterpenoids, now known, are acorone (60), β-vetivone (61), hinesol (62) and chamigrene (63) (Chart-XIII).

Another group of closely related sesquiterpenoids were isolated from the oil of *Cyperus scariosus*.[36] Terpenoids of novel structural types were also isolated from several other plants.



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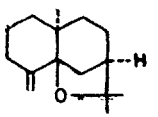

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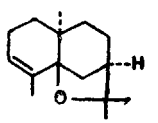

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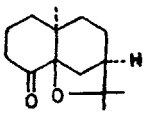

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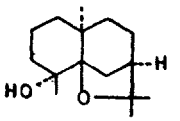

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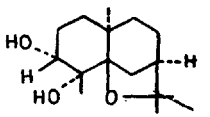

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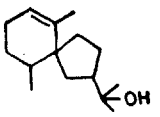
CHART XII



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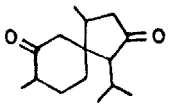

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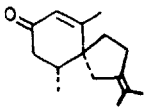

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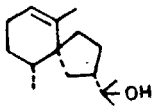

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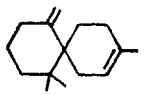

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CHART XIII

Along with several terpenoids of the usual and unusual types, the extractive of the roots of *Selimum vaginatum* yielded a closely related group of coumarins, including some furano and pyrano coumarins, one of which, jatamansin (selinene) (82) was related in structure to the visnadin group of cardiac drugs (83), to many of which it could be converted synthetically. The extractive in this case again proved to be a storehouse of chemicals[37–40] (ChartsXIV & XV).

There were many more fascinating compounds which were isolated by us during the course of our investigation, but I am not mentioning about all of them as the story may become too long and burdensome for some of the members of the audience.

I once again thank the Indian National Science Academy for selecting me for this lecture and the medal. It gave me an opportunity to convey my gratitude to

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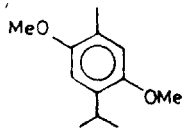

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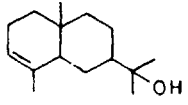

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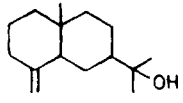

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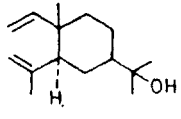

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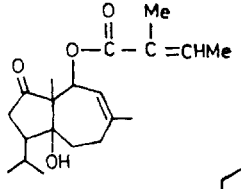

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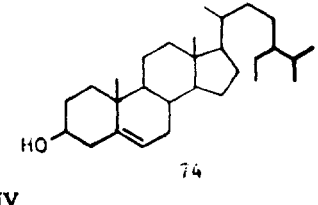

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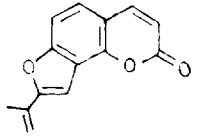
CHART XIV



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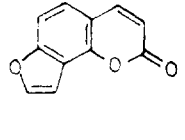

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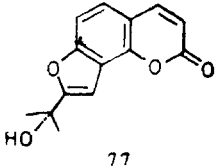

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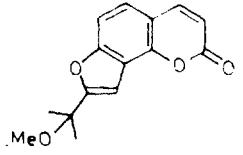

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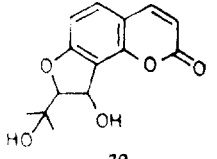

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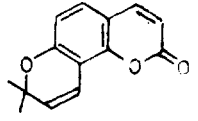

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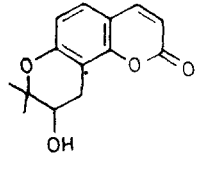

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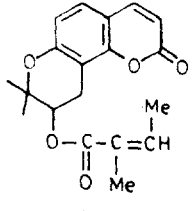

82

CHART XV

one of the most distinguished chemists of our land who achieved much but received much less, not even the minimum of creature comfort, which is a pity.

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