

Fascinating Organic Molecules from Nature

5. Using a Natural Product to Catch Fish! The Chemistry of Rotenoids

N R Krishnaswamy and C N Sundaresan



(left) N R Krishnaswamy was initiated into the world of natural products by T R Seshadri at University of Delhi. He has taught at Bangalore University, Calicut University and Sri Sathya Sai Institute of Higher Learning. He has the uncanny ability to present the chemistry of natural products logically and with feeling.

(Right) C N Sundaresan is currently an Associate Professor in the Department of Chemistry at the Sri Sathya Sai Institute of Higher Learning, Bangalore. His research interests are in synthesis of biologically active compounds, and pharmaceutical co-crystals.

Among the several ways of exploiting locally available plants in their day-to-day activities by primitive communities all over the world, catching fish for food was a major one. The plants used for this purpose included species of *Derris* and *Lonchocarpus* of the family *Leguminosae* (*Fabaceae*). The active principle, rotenone, is a pentacyclic isoflavanoid derivative. Several other closely related compounds are also known and these are together classified as rotenoids.

Introduction

Several plants have been used for catching fish (like curare for hunting birds and animals) from time immemorial by the natives of South America, Africa, Asia and the Pacific islands. Over a hundred such plants have been identified but the most widely used among them are species of *Derris*, *Lonchocarpus*, *Tephrosia*, *Mundulea* and *Millettia* belonging to the family *Fabaceae*. Different parts of these plants, such as leaves, bark, stem and seeds are used. The traditional method of catching fish using these plants involves pounding the plant part and scattering it on water. In the Hola technique used even now in Hawaii, seeds of *Tephrosia purpurea* (auhuhu) are powdered, packed in containers made out of grass or coconut palm leaves and placed in streams or tide pools. It is believed that the poison quickly loses its potency and therefore only freshly ground seeds are used and quickly dispersed. The fish which nibble at the material are stunned and are easily caught either by hand or in nets. The active principles of these plants belong to a group of plant secondary metabolites known as the rotenoids, the parent member of which is rotenone(1). Fish poisonous plants belonging to other families contain saponins, quinones, sesquiterpenes, etc. But, the rotenoids take the prime place as they can also be used as insecticides.

Keywords

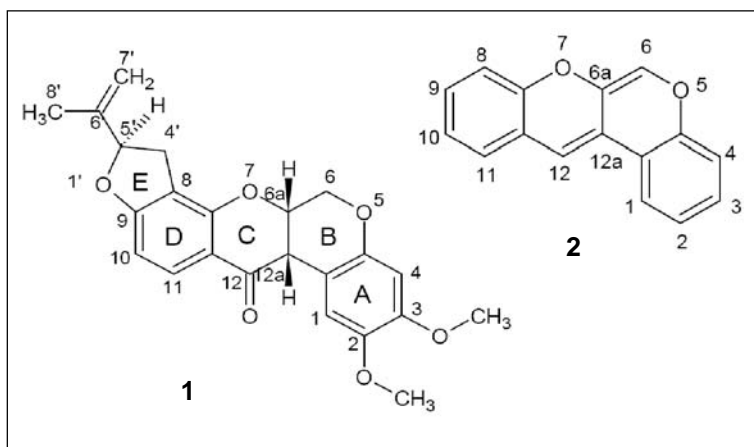
Rotenoids, rotenone, isorotenone and munduserone.



Structure of Rotenone

Rotenone (**1**) was first isolated by Geoffroy in 1892 from *Lonchocarpus nicou*. Twenty years later, Nagai obtained the same compound from *Derris chinensis*. In 1916, Ishikawa isolated rotenone from *Derris elliptica*. It has also been found to occur in other species of *Derris* as well as species of *Tephrosia*, *Lonchocarpus* and *Mundulea* among others. In 1928, Takei and Koide determined its correct molecular formula as $C_{23}H_{22}O_6$.

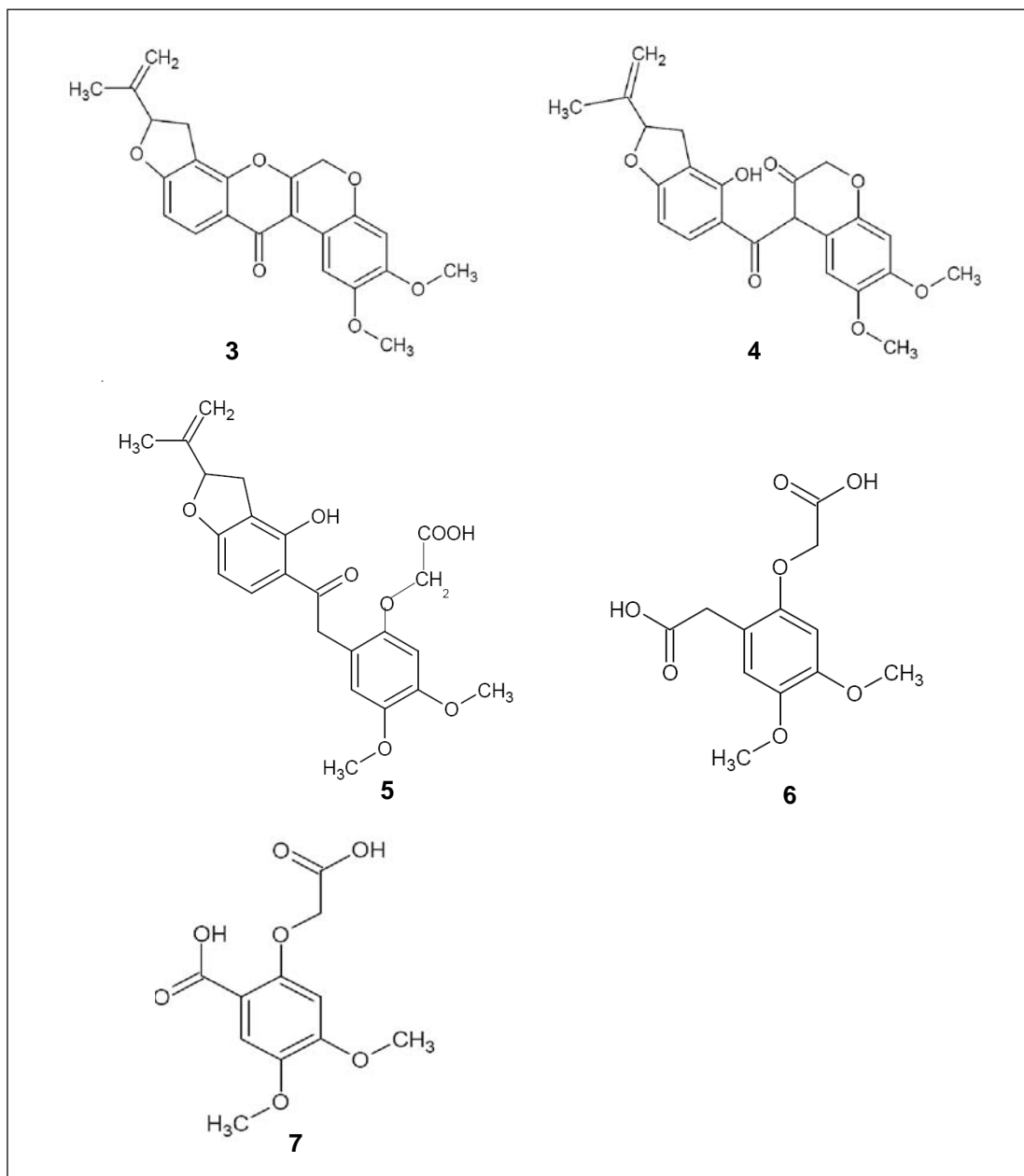
Four years later, Takei and co-workers in Japan, La Forge and Haller in USA, Butenandt in Germany and McCartney and Robertson in UK independently and simultaneously elucidated its structure as (**1**). Several other related compounds are also known and all of them possess the same fused tetracyclic skeletal structure named rotexen (**2**). Rotenone is 6a,12a,4', 5'-tetrahydro-2,3-dimethoxy-5'-isopropenylfuran-(3',2',8,9) 6H-rotexen-12-one. Rotenone can be readily dehydrogenated using oxidising agents such as potassium permanganate in acetone, potassium ferricyanide in methanol, perbenzoic acid in chloroform, manganese dioxide in acetone or iodine-sodium acetate in ethanol to obtain 6a, 12a-dehydrorotenone (**3**). On treatment with alcoholic potash, dehydrorotenone gives an unstable intermediate (**4**) which undergoes further hydrolytic cleavage to yield derrisic acid (**5**). The latter can be reconverted to (**3**) via (**4**) by dehydration. Derrisic acid, on oxidation with alkaline hydrogen peroxide,



Previous articles:

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4. Hunting with Poisoned Arrows: Story of Curare, Vol.18, No.3, 2013.

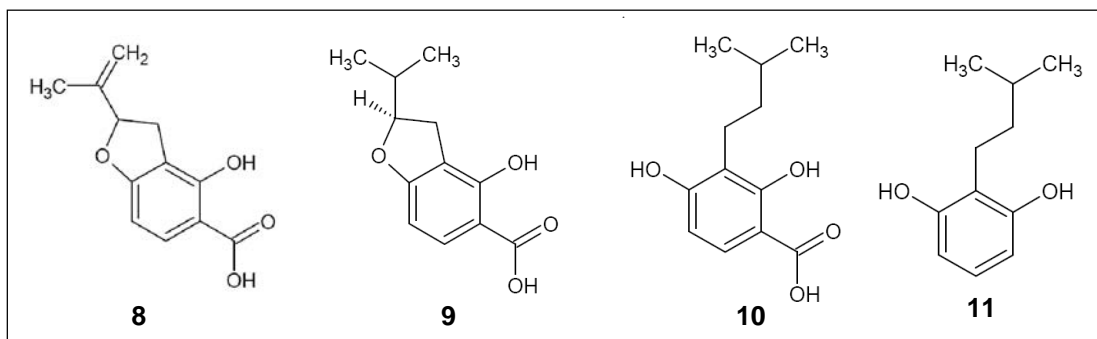
A French Botanist Emmanueal Geoffroy while traversing in French Guiana in 1892, isolated a chemical substance called 'Nicouline' from *Robinia nicou* now known as *Lonchocarpus nicou*. After his death in 1985, his work was published posthumously. In 1892, a pure crystalline compound named rotenone isolated from 'rohten' (a Japanese name for *Derris elliptica*) by a Japanese chemist, Nagai, was established in 1930 to be same as nicouline.



breaks down to derric acid (**6**) which on further oxidation gives rissic acid (**7**).

When rotenone is subjected to a vigorous treatment with hot alkali, it undergoes extensive degradation to yield tubaic acid (**8**).





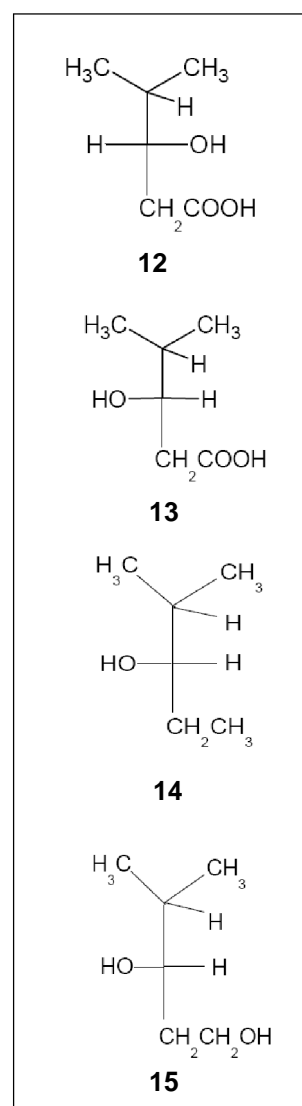
This salicylic acid derivative (it gives a violet colour with alcoholic ferric chloride) gives a dihydro derivative (**9**) on catalytic hydrogenation. Both (**8**) and (**9**) on prolonged hydrogenation yield the optically inactive tetrahydro tubaic acid (**10**). The latter on decarboxylation, by heating to its melting point, gives 2-isoamylresorcinol (tetrahydro tubanol) (**11**).

The reactions described above thus revealed the two parts of rotenone structure. Combining these data, the complete pentacyclic structure of rotenone was deduced.

Stereochemistry of Rotenone

Rotenone has three asymmetric centres, namely positions 5', 6a and 12a. The absolute stereochemistry of the compound was established by Birch and co-workers. Dihydro tubaic acid (**9**) on ozonolysis followed by further oxidation yielded a compound identified as (+)-3-hydroxy-4-methylpentanoic acid (**12**). Its relationship to D-glyceraldehyde was established in a roundabout manner. Thus, the enantiomer of (**12**), namely (**13**), which was more readily accessible by synthesis, was reduced to (-) 2-methylbutan-3-ol (**14**) via the diol (**15**); (**14**) had already been correlated with L-glyceraldehyde. Thus, the absolute configuration of position 5' in rotenone could be determined as R.

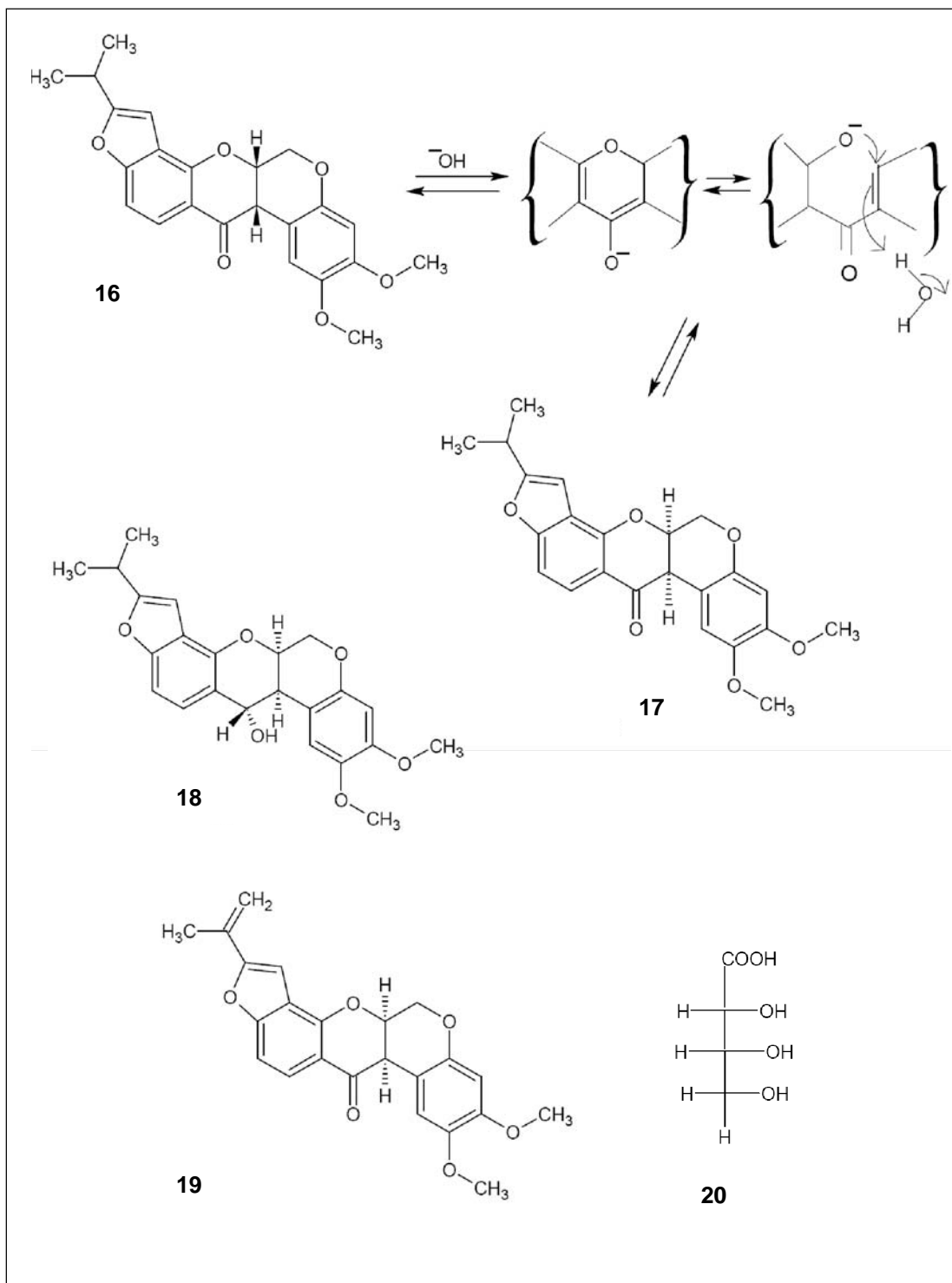
The other two asymmetric centres, 6a and 12a, at the junction of rings B and C, are common to all rotenoids, including those which lack the asymmetric centre 5'. In all rotenoids, these two rings are *cis*-fused as shown by the following observations.

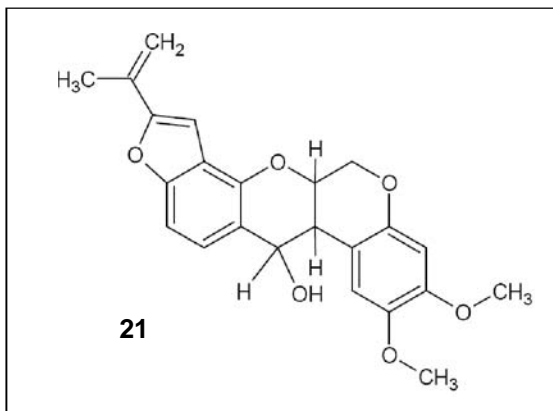


Naturally occurring laevorotatory rotenone gets converted into (-)-isorotenone (**16**) on treatment with sulphuric acid. This compound, in which position 5' is no longer asymmetric, undergoes facile racemisation under the influence of a mild base, such as sodium acetate in ethanol. This significant fact that racemisation occurs rather than epimerisation shows that inversion takes place at both 6a and 12a positions under the influence of the base catalyst. Racemic isorotenone on reduction with sodium borohydride gives a single product in high yield. The IR spectrum of the compound has an absorption band at 3566 cm^{-1} indicating the presence of a strong intramolecularly H-bonded OH group. This could only be the hydroxyl resulting from the reduction of the carbonyl group and is H-bonded to the oxygen at position 5. Models show that this is possible only if the B and C rings in isorotenone are *cis*-fused. Therefore (-)-isorotenone can be represented by structure (**16**) or the enantiomer (**17**). If (-)-isorotenone is (**16**) the reduction product should be (**18**). We shall see later that (**16**) is, indeed the absolute stereochemical structure of (-)-isorotenone. The probable mechanism for the racemisation of (**16**) is shown below. That rings B and C are *cis*-fused is also clearly brought out by the NMR spectra of rotenone and related compounds. In the spectrum of rotenone, H at 6a appears as a multiplet at $\delta 5.05$ and H at 12a is seen as a multiplet at $\delta 4.05$ ppm. The J value for coupling between these two hydrogen atoms has been determined as 4 Hz corresponding to a dihedral angle of 44° (from the Karplus equation) in accordance with *cis* fusion of rings B and C.

Like (-)-isorotenone, (-)-rotenone also undergoes a base-catalysed isomerisation to yield mutarotenone which is a mixture of diastereoisomers. Mutarotenone can be separated into (-)-rotenone and epi-rotenone (**19**). The latter, on treatment with an acid, isomerises to (+)-isorotenone (**17**). The absolute configuration at 6a was shown to be S by the isolation of D-glyceric acid (**20**) as one of the products of degradation of dihydrorotenone by ozonolysis followed by oxidation; the chiral carbon of (**20**) is 6a of rotenone. Thus, the absolute stereochemistry of rotenone is 5'(R)-, 6a-(S)-







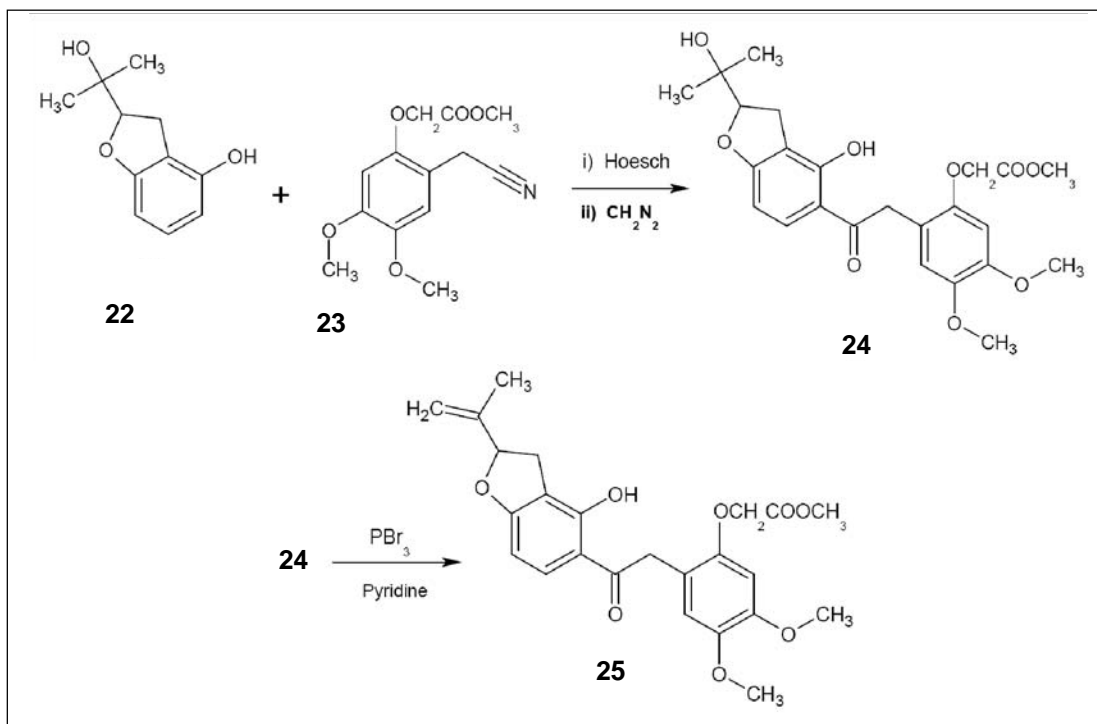
and 12a-(S). This assignment has also been confirmed using ORD and CD spectra of rotenone.

Synthesis of Rotenone

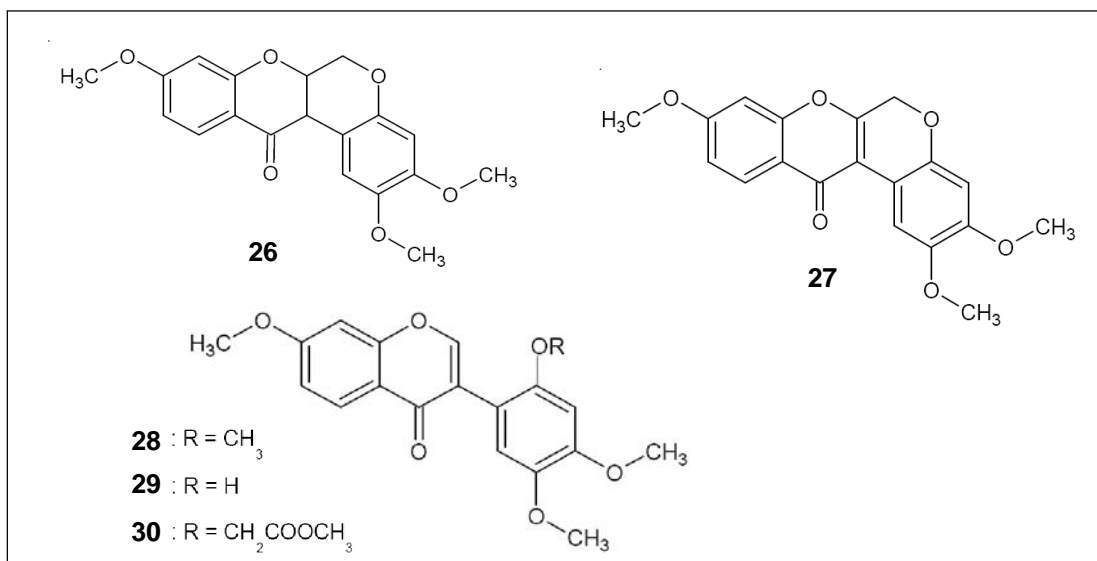
The conversion of derrisic acid (**5**) to dehydrorotenone (**3**) was readily achieved but the selective hydrogenation of the latter to rotenone proved difficult. Ultimately, in 1958, Miyano and Matsui succeeded in synthesising rotenone from dehydrorotenone by a two-step process involving reduction with sodium borohydride followed by Oppenauer oxidation of the resulting secondary carbinol (**21**). The entire sequence is given in *Scheme 1*. The first step is a Hoesch condensation between tubanol hydrate (**22**) and methyl derric acid nitrile (**23**). The resulting compound (**24**) on treatment with phosphorus tribromide in pyridine underwent dehydration to yield racemic methyl derrisate (**25**). On reaction with sodium acetate in acetic anhydride, (**25**) gave racemic dehydrorotenone (**3**). The meta rotenone obtained from (**3**) by the two-step reduction/oxidation mentioned above could be converted into (-)-rotenone by refluxing with carbon tetrachloride when the natural rotenone- CCl_4 separated out.

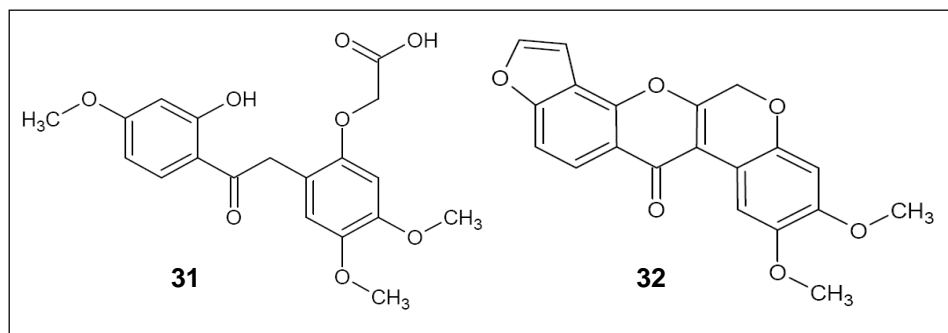
Rotenone is difficult to handle in the pure state, as it is sensitive to light and oxygen, quickly decomposing to less toxic products.

In 1967, Seshadri and co-workers reported a synthesis of a simpler member of the rotenoid family, namely, munduserone (**26**) via dehydromunduserone (**27**). A key step in this synthesis was the selective demethylation (a technique developed and extensively exploited by the Seshadri school) of the 2'-methoxyl



group in 7,2',4',5'-tetramethoxyisoflavone (**28**). This was achieved by using anhydrous aluminium chloride in acetonitrile. The product (**29**) was treated with methyl bromoacetate in the presence of anhydrous potassium carbonate. The resulting ester (**30**) was

Scheme 1.




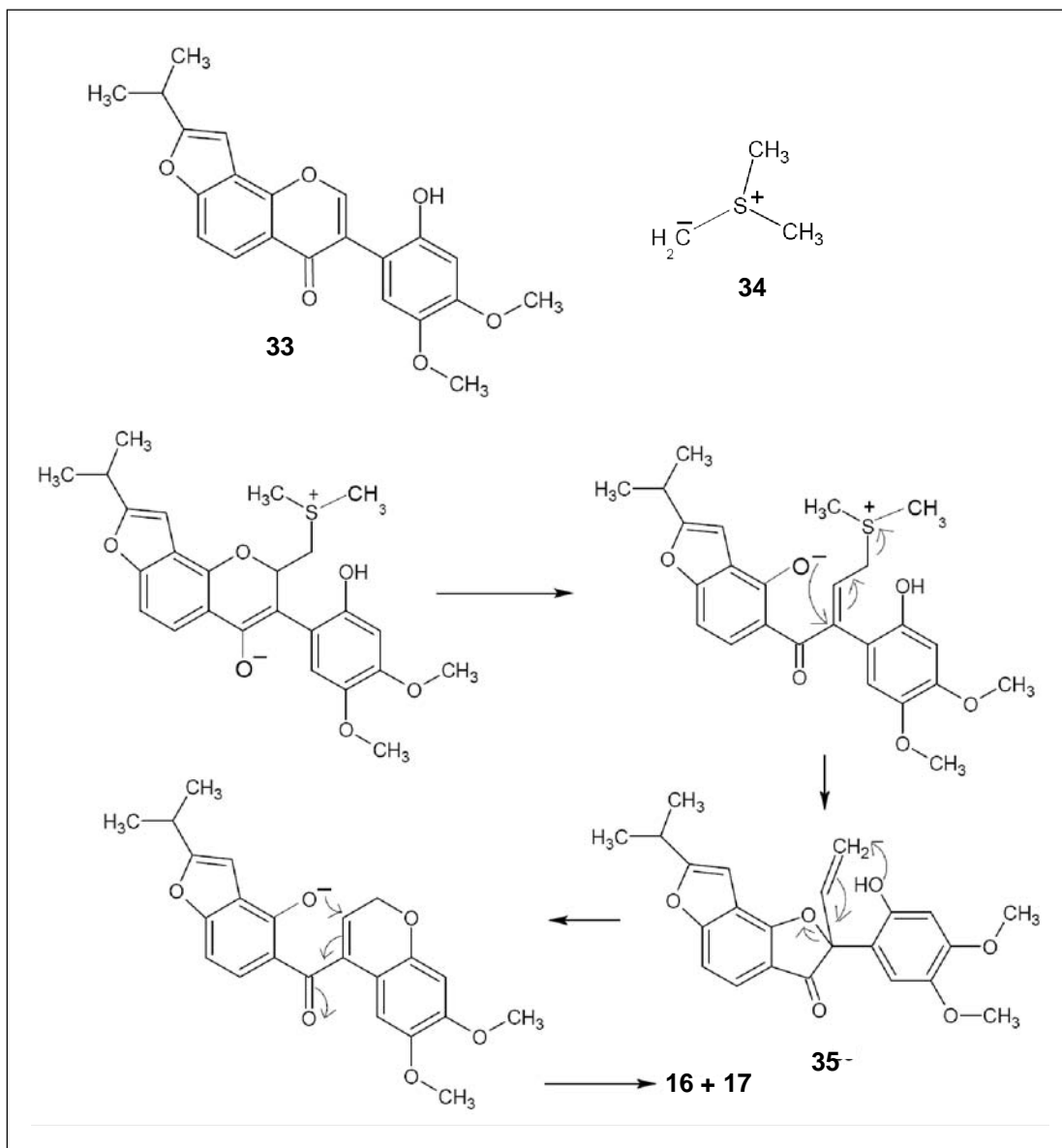
subjected to a controlled alkaline degradation to obtain the desoxybenzoin derivative (**31**); this is a well-established procedure for the conversion of isoflavones to the corresponding desoxybenzoins by a retro Claisen–Schmidt reaction. After methylation with diazomethane, (**31**) could be readily converted into dehydromunduserone (**27**) by heating with sodium acetate and acetic anhydride. Using this strategy, Sesahdri and his co-workers also synthesised the pentacyclic compound, dehydroelliptone (**32**). A novel feature of this method is the involvement of a backward step to facilitate further onward movement.

Subsequently, Crombie and co-workers reported a novel and elegant synthesis of racemic isorotenone (**16** + **17**) using the isoflavone (**33**) as the starting material. This compound, on treatment with dimethylsulphoxonium methylide (**34**) gave the vinyl coumaranone (**35**) as shown in *Scheme 2*. On treatment with pyridine, (**35**) underwent a rearrangement to yield the target compound. Using this method, other rotenoids, including rotenone, have been synthesized.

Other Rotenoids

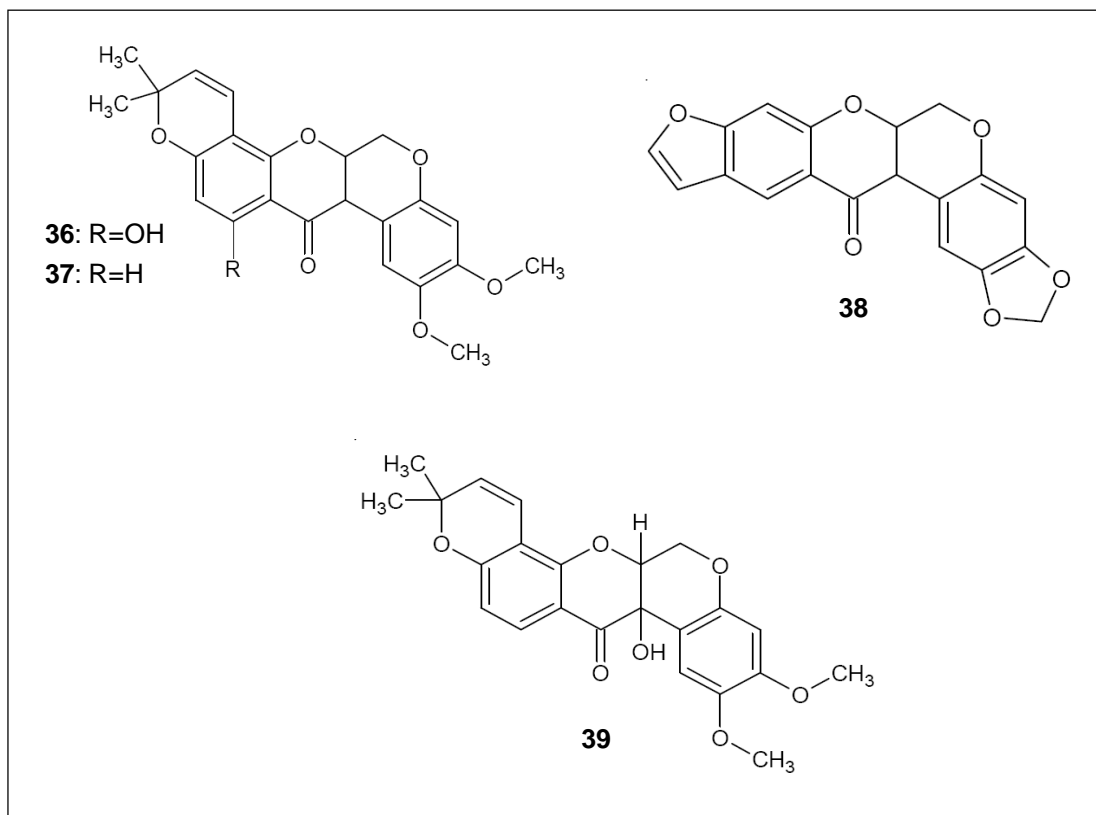
Munduserone (**26**) was mentioned earlier. This tetracyclic compound is isolated from the bark of *Mundulea sericea*. Like rotenone, α -toxicarol (**36**) is also a pentacyclic compound. It occurs in several species of the genus *Tephrosia* (*T. toxicara*, *T. obovata*, etc.) as well as in species of *Derris*, such as *D. elliptica*. Deguelin (**37**), which often co-occurs with α -toxicarol, lacks the hydroxyl group at position 11. *Pachyrhizus erosus*, commonly

Small-scale sampling with rotenone is used in studying the biodiversity of marine fishes to collect cryptic and hidden fishes, which form a vital component of shoreline fish communities.



known as Yam beans, Mexican turnip, Mexican Yam or Jicama, contains several isoflavonoid compounds, including the rotenoid, pachyrhizone (**38**). Tephrosin (**39**) is interesting in the sense that it has a hydroxyl instead of H at position 12a in deguelin. This compound has been isolated from the seeds of *Tephrosia purpurea* and *T. vogelii*.

Scheme 2.



Conclusions

Interest in the rotenoids is continuing as they are considered to be comparatively safe insecticides and leave no toxic residues. *Tephrosia vogelii* is cultivated in several parts of Africa to enrich soil through biological nitrogen fixation. The abundant foliage can be easily collected. The leaves contain several rotenoids and possess considerable insecticidal activities. Ongoing research has shown that these rotenoids can be used to control cowpea weevils, ticks and mites. They also show larvicidal activity and potential for controlling dengue fever. Biotechnological techniques have also been explored for improving the rotenoid content of the leaves of *T. vogelii*. Thus, from the jungles of South America and Africa, the rotenoids have emerged not only as fish poisons but also as useful insecticides with a potential future.



Suggested Reading

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