綜 説

Advances in Pyrethrum Chemistry Yuzo Inouye (Institute for Chemical Research, Kyoto University)

31. 除虫菊の化学の進歩

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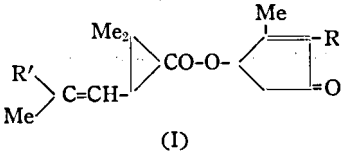
During the decade that has elapsed since publications of some comprehensive reviews[1~5], our knowledge of the chemistry of pyrethrum has greatly increased. It has been found desirable, therefore, to devote some pages of the *Silver Jubilee Issue* of this Journal to the chemistry of pyrethrum.

The disclosure of the heterogeneity of the pyrethrolone[6,7] has made much of the earlier degrative and synthetic works carried out prior to 1945, including the outstanding ones of Staudinger and Ruzicka[8], of dubious value. The evidence for the existence of and the currently accepted structures of the four insecticidal constituents, cinerins-I, II, pyrethrins-I and II, has been summarised in the above-cited reviews, to which the reader is referred. It is chiefly with the subsequent developments in pyrethrum chemistry that the present article is concerned. Literature has been consulted up to September of 1960.

As the pyrethrins are *esters*, both structural and synthetic problems conveniently resolve themselves into those of the *ketoalcohol* moiety and those of *chrysanthemic* or *pyrethric acids* moiety and consequently, this account will conveniently follow the separate part of the pyrethrins.

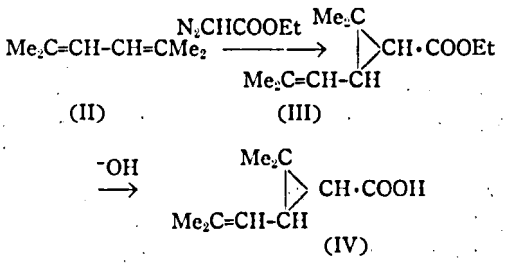


(I)

	R	R′
Pyrethrin-I,	$-CH_2-CH=CH-CH=CH_2$,	-Me
Pyrethrin-II,	$-CH_2-CH=CH-CH=CH_2$,	-COOMe
Cinerin-I,	$-CH_2-CH=CH-Me$,	-Me
Cinerin-II,	$-CH_2-CH=CH-Me$,	-COOMe

Chrysanthemic acid

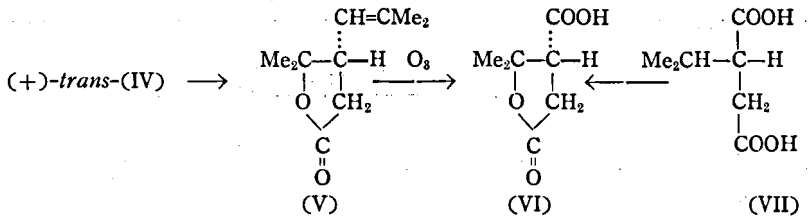
can exist in four stereoisomers due to the two asymmetric carbon atoms in the cyclopropane ring and the naturally derived acid has been shown to have the (+)-*trans*-configuration. All isomeric acids have been synthesised, separated and optically resolved by Harper[9~11].



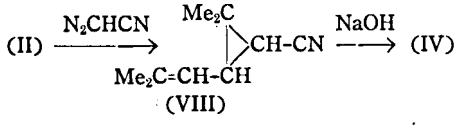
(II) (III) (IV)

Having been supplied with 2,5-dimethylhexa-2,4-diene (II) from Reppe synthesis, the improved method of synthesis has now enabled one to manufacture chrysanthemic acids on commercial basis for incorporation as a component of allethrin [(I) : R= $-CH_2-CH=CH_2$, R′=Me]. Extensive and elaborate studies on esterification, lactonisation, hydration and catalytic hydrogenation of the chrysanthemic acids have been worked out by Harper[12~15]. Of these achievements, the elucidation of the structure of (-)-pyrocin[16], originally isolated from the pyrolysis of pyrethrum by Japanese worker[16~18], is of particular interest. (-)-β-Isobutenylisohexano-γ-lactone (V) was deduced to this lactone and the ozonolysis to give (+)-terebic acid (VI) has made possible the correlation of the absolute configurations of the optically active chrysanthemic acids to (-)-glyceraldehyde through the key intermediates, (-)-isopropylsuccinic (VII) and (-)-methylsuccinic acids.

Interrelations of the epimeric chrysanthemic acids have been completed by the conversion of (+)-*cis*-chrysanthemic acid into (+)-pyrocin, thereby revealing the fact that the enantiomeric (-)-*cis*-chrysanthemic acid is the $C_{(1)}$ epimer of



(+)-*trans*-acid[19]. Thus, (+)-*trans*-, (−)-*trans*-, (+)-*cis*-, and (−)-*cis*-chrysanthemic acids have the (1*R*:3*R*)-, (1*S*:3*S*)-, (1*R*:3*S*)- and (1*S*:3*R*)-configurations in the order respectively.



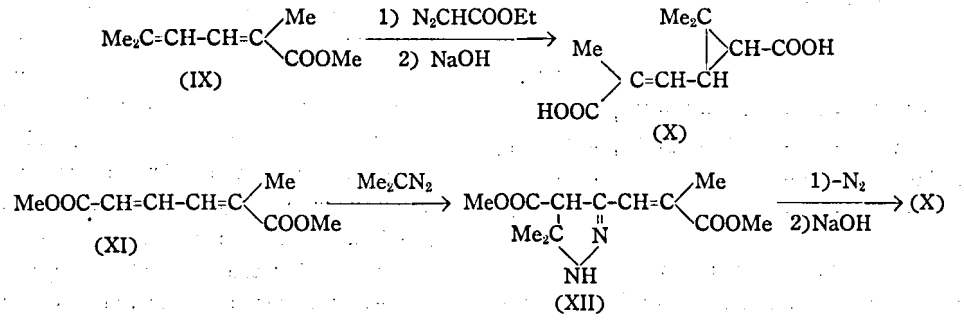
Another modified route to this acid has been devised[20], involving the addition of diazoacetonitrile to 2,5-dimethylhexa-2,4-diene (II), followed by alkaline hydrolysis of the resultant chrysanthemonitrile (VIII) into exclusively *trans*-chrysanthemic acid. Successive homologations of optically active and racemic chrysanthemic acids by means of Arndt-Eistert reaction yielded the next higher homologous acids with *trans*-isomers, whilst with the *cis*-acid, an anomalous ring expansion leading to a cyclobutane derivative has been observed[21~24]. Modified chrysanthemic acids such that contain substituted aryl-, halogenated-[25,26] and piperonyl-side chains[27], have been prepared and their allethronyl esters have been tested for insecticidal activity. Methyl (±)-*cis*-chrysanthemate was converted by the action of sodium *t*-amylate in benzene into the (±)-*trans*-isomer[28]. The geometrical stereochemistry of the cyclopropane ring of chrysanthemic acid portion in both natural and synthetic rethrins-I was readily decided by the characteristic bands in infrared spectra[29]. Lithium aluminum hydride reduction of chrysanthemic acids yielded the corresponding alcohols, chrysanthemol[30], and some of its esters have been claimed to have insecticidal activity[31].

Chrysanthemum dicarboxylic acid

must have either *cis*- or *trans*-configuration about the side chain double bond in addition to that of cyclopropane and therefore, eight stereoisomeric forms——four pairs of *trans, trans*-; *trans, cis*-; *cis, trans*- and *cis, cis*-racemates——are possible. Three isomeric acids except *cis, cis*-form, have been synthesised and their geometrical configurations were assigned[32~49]. By treating *trans*-2,5-dimethylsorbic acid ester (IX) with ethyl diazoacetate, (±)-*trans, trans*- and (±)-*cis, trans*-chrysanthemum dicarboxylic acids, both having the *trans*-side chain double bond, were obtained in preponderance of the former. The *trans*-configuration of the starting dimethylsorbic acid was evidenced in elaborate works[35,36,44,45].

In an alternative route to this acid[50~54] which involved the addition of dimethyldiazomethane to the ester of isomeric α-methylmuconic acids (XI), followed by thermal decomposition of pyrazoline intermediate (XII), (±)-*trans, cis*- and (±)-*trans, trans*-chrysanthemum dicarboxylic acids were obtained.

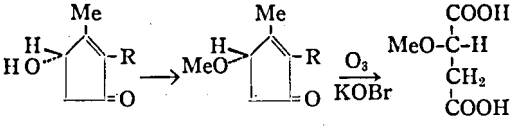
This affords another evidence for the geometry



of chrysanthemum dicarboxylic acid. Of the three racemates thus obtained, the *trans, trans*-acid was equated with the naturally derived (+)-acid by infrared spectra and the optical resolution of the synthetic acid completed the total synthesis of chrysanthemum dicarboxylic acid[40,46]. Selenium dioxide oxidation of chrysanthemates gave aldehydic esters, which upon treatment with silver dioxide, yielded chrysanthemum dicarboxylic acids [55,56]. This conversion of (+)-*trans*-chrysanthemic acid into (+)-*trans, trans*-chrysanthemum dicarboxlic acid revealed that both of the chrysanthemum carboxylic acids are of the same optical series and have the same (+)-(1*R* : 3*R*)-configuration with regards the two asymmetric carbon atoms. This interrelation was also obtained by the ozonolysis of methyl (+)-*trans*-chrysanthemate and of methyl (+)-*trans, trans*-chrysanthemum dicarboxylate to give equally the same (1) methyl (2) hydrogen (−)-*trans*-caronate[57]. Pyrethric acids were prepared by the partial hydrolysis of dimethyl (±)-*trans, trans*-, (±)-*cis, trans*- and (+)-*trans, trans*-chrysanthemum dicarboxylates and the esterifications with allethrolone afforded the first synthetic rethrins-II for testing the insecticidal activity[49]. Methyl (+)-*trans, trans*-chrysanthemum dicarboxylate, when treated with potassium methoxide in absolute methanol, racemised into exclusively (±)-*trans, trans*-isomer. A dicarbanion was postulated as the transition intermediate in this racemisation and the *cis*→*trans* inversion of chrysanthemate by the action of sodium *t*-amylate[29] seems to have some common features in mechanism with this racemisation.

Pyrethrolone (XIII-a) and cinerolone (XIII-b)

constituting the ketoalcohol moiety of the pyrethrins, each possess one asymmetric carbon at 4-position and a double bond capable of *cis-trans* isomerism in 2′-position of the side chain and, therefore, four stereoisomers are possible for each. The absolute configuration of the asymmetric carbon in both of the naturally derived cyclopentenolones was established to be the (+)-*S*-configuration by converting these (+)-ketoalcohols into the corresponding (+)-methylethers (XIV), followed by successive oxidations with ozone and then hypobromite to give equally the same (−)-methoxysuccinic acid (XV) which had been correlated with (−)-glyceraldehyde[59~62].

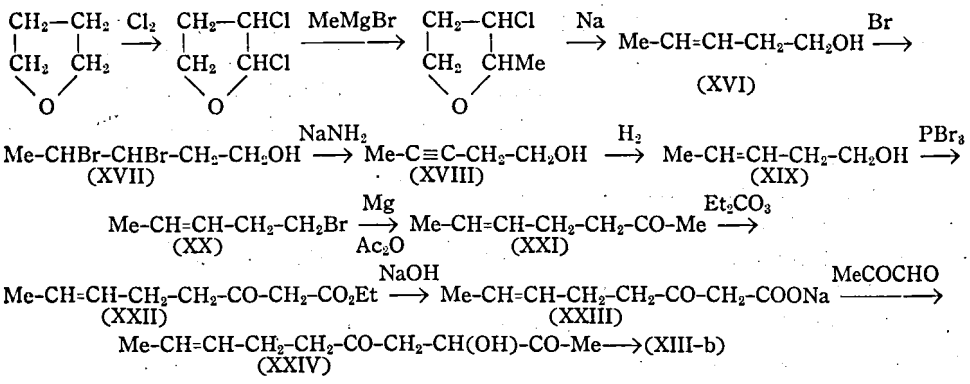


(XIII) (XIV) (XV)

a, pyrethrolone, R= $-CH_2-CH=CH-CH=CH_2$

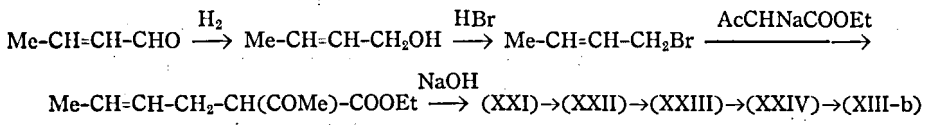
b, cinerolone, R= $-CH_2-CH=CH-Me$

In earlier works, cinerolone and pyrethrolone were isolated in both (+)- and (±)-forms, but the latter might probably be artefact which was formed during isolation procedures and only the (+)-form occurrs in the natural esters. Cinerolone and its derivatives are rather stable to heat, whilst pyrethrolone and its derivatives undergo thermal isomerisation with migration of the side chain double bonds into conjugation with the cyclopentenone ring. These isomerisations are accompanied by an increase in the negative rotations of the compounds and they probably explain the conflicting rotations previously reported for these compounds and resynthesised pyrethrins[63~72]. The fifth and sixth pyrethrolone semicarbazones were considered to be formed by undergoing this change during rigorous fractional distillation. This structural change can not take place without affecting the rotaions as well as the geometry of the side chain double bond. It is no exaggeration to say that after the chemical structures had been determined, works on the natural rethrolones were concentrated to the elucidation of the geometry of the side chain double bond. Our present knowledge may reveal that the disagreement found between the synthetic and the natural rethrolones may reasonably ascribed to the heterogeneity of the natural pyrethrolone preparations caused by contamination of the (±)-forms and/or those with rearranged 1′-double bond. The synthesis of (±)-cinerone and its homologues[73] was the first to confirm the cyclopentenone structure presented by LaForge[74~76]. Subsequently, 3-methyl-2-*n*-alkylcyclopent-2-en-1-ones were brominated with N-

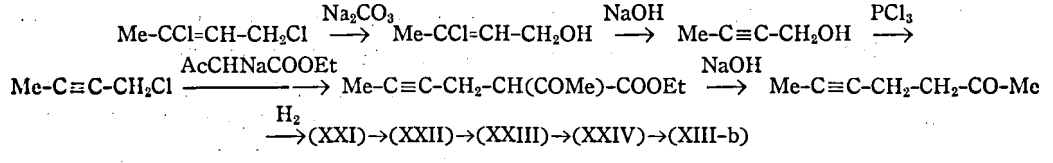


bromosuccinimide to 4-bromoketones, which were converted via acetoxyketone into (±)-4-hydroxyketones[77~81]. By this means were prepared (±)-dihydrocinerolone and (±)-tetrahydropyrethrolone[82], thereby providing the first synthetic evidence for the 4-position of hydroxy group in natural rethrolones. The synthetic *trans*-cinerone was not identical with the cinerone derived by degradation of natural cinerolone, pointing to this having the *cis*-configuration. Harper devised the fourteen stage syntheses of cinerolone and cinerone, whose identity with naturally derived racemic compounds was established by direct comparison of the semicarbazones and acetate semicarbazones, as well as of their infrared spectra[51,83~88]. Soon after, an improved ten stage synthesis of cinerolone, involving *n*-pent-3-yn-1-ol (XVIII) as the key intermediate, was devised[88].

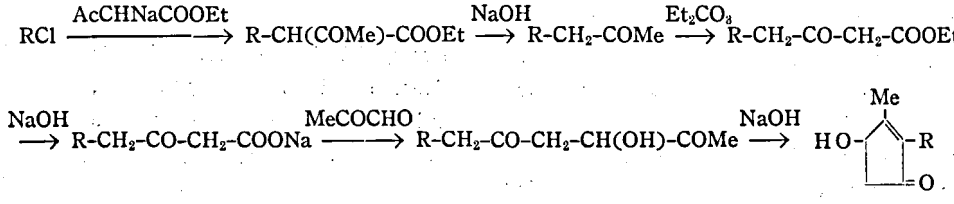
(±)-*trans*-Cinerolone was synthesised by the following route[81,85]:



The lack of identity of (±)-*trans*-cinerolone with naturally derived racemic cinerolone which was shown by comparison of semicarbazones, acetate semicarbazones and infrared spectra[89], provided further evidence for the configurations assigned to these compounds. By adopting this synthesis to that of the *cis*-isomer, Harper has synthsised (±)-*cis*-cinerolone in an improved overall yield[88].



The resolution of synthetic (±)-*cis*-cinerolone into its (+)- and (−)-enantiomers by means of (+)- or (−)-*trans*-chrysanthemate semicarbazones and the subsequent esterification with enantiomeric *trans*-chrysanthemic acids completed the total synthesis of cinerin-I[90]. When the starting alkenyl chloride, RCl, is readily accessible, the production of the corresponding alkenyl-rethrolone is greatly facilitated in the following six stage synthesis in actual operation.



Many analogues of cinerolone have been synthesised in this way and have been esterified with the chrysanthemic acids to give analogues of cinerin-I[91~95]. Among these discoveries, the commercial production of allethrin[90,96~98] has been developed and now substantial quantities have been marketed at a pricecom parable to that of pyrethrum. In the similar manner to that of cinerolone, allethrolone was resolved[99] and esterified with enantiomeric *trans*-chrysanthemic acids to afford four optical isomers of *trans*-allethrins[100].

A crystalline allethrin, α-dl-*trans*-allethrin, was shown to be a racemic compound of (+)-allethronyl (−)-*trans*-chrysanthemate and (−)-allethronyl (−)-trans-chrysanthemate[99,101]. This is made to introduce *cis*-pent-2, 4-dienyl system into cyclopentenolone, the last pending and the most difficult problem in pyrethrum chemistry. Using the intermediates elaborated in the preliminary work[104~106], Crombie has achieved the synthesis of (±)-*cis*-pyrethrolone[105], which was found to be identical with pyrethrolone B-2 of natural origin. The diasteroisomeric mixture of esters (+)-*cis*-pyrethronyl (+)-*trans*-chrysanthemate and (−)-*cis*-pyrethronyl (−)-*trans*-chrysanthemate was prepared, the former being the natural pyrethrin-I.

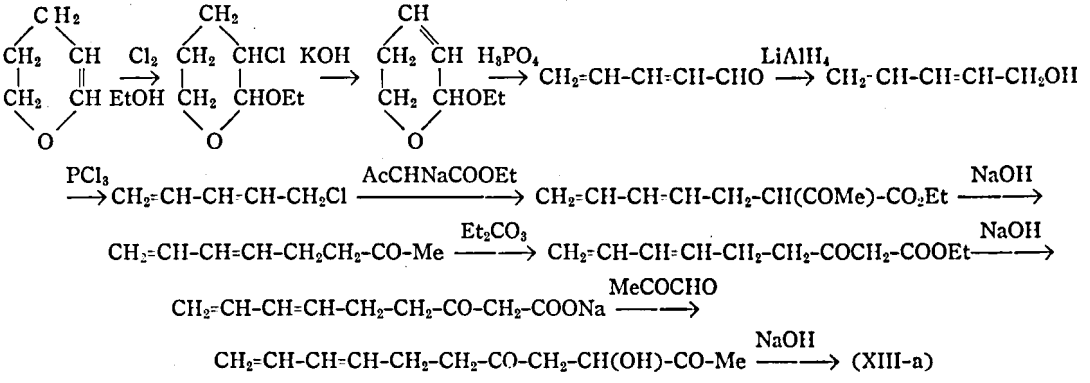
With many homologues and analogues, varieties of stereoisomers of the pyrethroids now made an useful standard for both chemical and bio-assays of the pyrethroids.

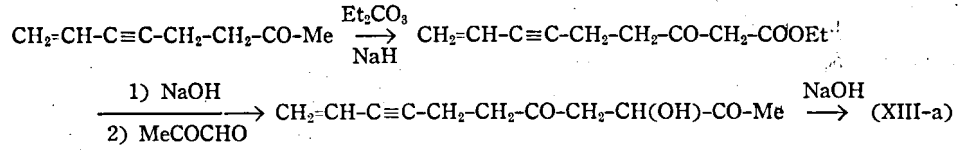
Following a similar course to that of cinerolone, Harper has synthesised (±)-*trans*-pyrethrolone as well as (±)-*trans*-pyrethrone[102].

Comparison with naturally derived pyrethrolone B-2 showed lack of identity and hence, it was concluded that pyrethrolone B is *cis*-pyrethrolone. This configuration so assigned was further confirmed by the complete identity of *cis*-jasmone with naturally derived (±)-dihydropyrethrone[103]. Esterification of (±)-*trans*-pyrethrolone with (+)-*trans*-chrysanthemic acid gave a *trans*-pyrethrin-I with considerable activity. Endeavour has been readily available for testinging insecticidal activity, the relationship between chemical structures and insecticidal activity has become revealed[1,4,108]. In particular, the stereochemical conformation theory, exemplified by a complete set of stereoisomeric allethrins and closely strucured modifications, has been greatly developed in the light of the established stereochemistry of pyrethroids[98,109].

Absorption and metabolism by insects of pyrethroids were followed by means of the modern tracer technique with ^{14}C-labelled pyrethroids[110~112].

Many attempts have been made to solve the vexed question of



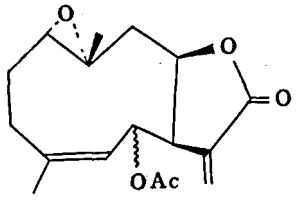


but little has so far been achieved. The Seil titrimetric method[113], formerly widely used, was made obscure because of its substantial faults. The so-called mercury reduction method is currently employed, but correct results are obtained only by strict adherence to the specified conditions, which, like the factor used to calculate the results, are quite empirical. Some important versions of this method were proposed but even these modifications were far from making it perfect[114~128]. Attempts have also been made to utilise spectrophotometry to determine the total pyrethrins as such and an UV-method was initiated by Beckley [129~132] and was developed by Shukis[133] in combination with a high vacuum technique. The IR-spectrophotometric method[134,135], polarographic[148], colorimetric and chromatographic methods[136~147] have been proposed for their claimed accuracy, reproducibility, convenient and speedy performance, but their practical application to the assay of pyrethroids is probably limited. Since the problem of pyrethrum analysis is a most entangled one, it can not be exhausted in this brief account and the reader should refer to the summaries by other authors[149~157].

MISCELLANEOUS COMPOUNDS

other than the pyrethroids have been reported to be present, free or combined, in pyrethrum.

Pyrethrosin was first isolated by Rose and Haller as early as 1937[159~160], but its structural problem has no further been prosecuted until 1957. Barton has deduced the following decagonal structure to this lactone[161~2].



Pyrethrosin is the *first decagonal terpenoids* found in nature and is of particular interst in its biogenetic significance as a possible precursor of most of the bicyclic sesquiterpenoids. β-Amyrin or a related triterpene[163], ceryl alcohol[163], hentriacontane and nonacosane[163], all the normal paraffins from C_{24}-C_{26} and possible higher members [164] an irritant phenolic compound[165], tiglic[166], palmitic and linoleic acids[167], chlorophyllin mixture[168], light oil with characteristic odour[169] and a hydrocarbon $C_{19}H_{40}$[169] have been detected in pyrethrum.

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32. Rotenoids の化学

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デリス根は古くから魚毒として知られ，また除虫菊や煙草と並んで有力な殺虫剤でもあって，特にその有効成分の代表的なものである rotenone は昆虫に対して経口毒としては砒酸鉛よりも強く接触毒としては nicotine の十数倍といわれる反面，温血動物には無害であるという特性のために多くの研究者の注目をひいた天然物である．デリスやその他の植物から rotenone をはじめとして，これと類似の化学構造の物質が次々と単離され，これらは総称して *"rotenoid"* と名付けられている．Rotenoids についてはすでに二，三の綜説[1~4]があるが，中でも宮島著の成書「デリス」[3] は内容の完璧さにおいて他の追随を許さぬものであり，1940年頃までの rotenoids に関する化学的研究が漏れなく記載されている．したがってここではそれ以降に行われた rotenoids の研究に重点をおき特に合成化学の面を中心として記述する．

まず rotenoids の化学的研究の歴史を概観するとデリス根の有効成分については1902年永井[5]がその主成分を単離し rotenone と命名して本格的な研究の端緒が開かれ，1928年武居[6]によって rotenone の正確な分子式 $C_{23}H_{22}O_6$ が与えられて漸くその化学構造の研究が活潑となり，1932年に至って武居等[7]，Butenandt 等[8]および LaForge 等[9]の日・独・米三国の研究陣によってそれぞれ独立に全く同じ構造式が出されて rotenone の化学構造が決定した．一方 rotenone の構造と共に種々の rotenoids も新しく単離され rotenone の異性体である deguelin などの化学構造も rotenone の構造を基礎として順次決定されていった．このようにして rotenoids の構造が明かになって以後は主として Robertson 等によりその合成の研究が続けられて多くの成果[10]がえられたにもかかわらず rotenoids の全合成はできなかった．1958年になって宮野等[11]によって dehydrorotenone を rotenone に還元する巧妙な方法が発見されて以来はじめて rotenoids の全合成の道が拓け，1959年には宮野等[12]は dihydrorotenone の全合成に成功し 1960 年には深海等[13]は deguelin の，