

# CRC Handbook of Terpenoids

Diterpenoids

Volume IV: Tetracyclic and  
Pentacyclic Diterpenoids

Editor

Sukh Dev

Renuka Misra

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**CRC Press, Inc.**  
**Boca Raton, Florida**

**Library of Congress Cataloging in Publication Data**

Main entry under title:

CRC handbook of terpenoids—Diterpenoids.

Includes bibliographies and index.

I. Terpenes—Handbooks, manuals, etc. I. Dev, Sukh, 1923- II. Misra, Renuka. III. Title:

C.R.C. handbook of terpenoids—Diterpenoids.

QD416.7.C7 1986 547.7'1 84-17624

ISBN 0-8493-3603-1 (set)

ISBN 0-8493-3604-X (v.I)

ISBN 0-8493-3605-8 (v.II)

ISBN 0-8493-3606-6 (v.III)

ISBN 0-8493-3607-4 (v.IV)

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Direct all inquiries to CRC Press, Inc., 2000 Corporate Blvd., N.W., Boca Raton, Florida, 33431.

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International Standard Book Number 0-8493-3603-1 (set)

International Standard Book Number 0-8493-3604-X (v.I)

International Standard Book Number 0-8493-3605-8 (v.II)

International Standard Book Number 0-8493-3606-6 (v.III)

International Standard Book Number 0-8493-3607-4 (v.IV)

Library of Congress Card Number 84-17624

Printed in the United States

## PREFACE

Around 1950, a new era in natural products chemistry can be considered to have begun. Aided by more and more effective techniques of separation and synthesis and increasingly useful spectroscopic methods, structures of natural products have been accumulating at an overwhelming rate. This is certainly true of terpenoids, one of the most widely distributed and important class of the so-called secondary metabolites. Terpenoids have singularly enriched organic chemistry by its variety of structural types, by its wealth of 'unexpected' reactions, rearrangements and spectral features, and by offering exciting targets for synthesis. Much imaginative experimental work has been invested in exploring their natural pathways. Recent years have revealed an increasingly important biological role for several of its members.

In view of these developments workers in this area have often felt a need for a sort of Handbook, pinpointing salient features of the known information, in a form which is at once accessible and readable. The present work is an effort in that direction.

A total of 5 sections covering the following categories are planned:

- Monoterpenoids
- Sesquiterpenoids
- Diterpenoids
- Triterpenoids
- Sesterterpenoids, polyprenoids, and meroterpenoids.

Steroids, carotenoids, and certain classes of meroterpenoids (for example, indole alkaloids) have been kept outside the purview of the present work. Each section will consist of two or more volumes. Two volumes covering Monoterpenoids were published in mid-1982.

The present work covers Diterpenoids in four volumes:

- Volume I: Acyclic and Monocyclic
- Volume II: Bicyclic
- Volume III: Tricyclic
- Volume IV: Tetracyclic and Pentacyclic

Every effort has been made to cover naturally occurring compounds which have appeared in accessible literature till the end of 1979. However, it will be unrealistic not to expect errors and omissions in a work of this magnitude and the authors will be grateful to discerning readers for drawing their attention to these. Besides, the catalog section which forms the bulk of the work, a chapter entitled *General Introduction*, which surveys the development of diterpenoid chemistry, has been included. A selected list of references to books and reviews dealing with various aspects of diterpene chemistry has also been included and should prove useful.

The authors would like to express their thanks to Dr. Hemant A. Patel for drawing most of the structures, to Shri. Arun P. Dindorkar for inking these, to Shri. R. Kuttappan for typing the entire manuscript, and to Shri. J. R. Patel for checking the same. Finally, I would like to thank Shashi Prabha, my wife, for all the understanding and moral support which made the undertaking of this work possible.

Sukh Dev  
Nandesari, Vadodara

## THE EDITOR

**Sukh Dev** was born in Chakwal, now in Pakistan, in 1923. He studied at D.A.V. College Lahore (M.Sc.), and later at Indian Institute of Science, Bangalore (Ph.D., D.Sc.). He served as a Research Associate and Lecturer at the Indian Institute of Science, and for 1 year (1957) as a Research Associate at the University of Illinois, Urbana, before taking over as Head of the Division of Organic Chemistry (Natural Products) at the National Chemical Laboratory, Poona, in 1960. In 1974, he moved to the newly created Malti-Chem Research Centre, as its Research Director, a position he holds at present.

Sukh Dev has been a Visiting Professor at the Stevens Institute of Technology, Hoboken in 1968, at the University of Georgia, Athens in 1968, and at the University of Oklahoma, Norman in 1970 to 1971. He has been an invited speaker at several International Symposia on natural products chemistry and at many Universities/Research Institutes in several countries of the world. He is the recipient of many national awards and in 1980 received the Ernest Guenther Award of the American Chemical Society. He was elected President of the Indian Chemical Society for the term 1978 to 1979.

His research interests include natural products chemistry, especially terpenoids, nonbenzenoid aromatic systems, organic reactions and, new technology development. He is the author of over 250 research papers and holds 48 patents.

## ACKNOWLEDGEMENTS

This work would not have been possible without the whole-hearted support, cooperation, understanding and encouragement of my friends and colleagues.

I would like to especially acknowledge Dr. O. E. Edwards of the National Research Council, Ottawa, Canada; Prof. E. J. Corey of Harvard University, Cambridge, Massachusetts, and Dr. Gopal M. Bhatnagar of Johns Hopkins School of Medicine, Baltimore, Maryland, for library and xeroxing facilities.

For the inspiration, valuable advice and constructive suggestions during the preparation of this manuscript, I thank Prof. K. L. Rinehart, Jr. of University of Illinois, Urbana, Illinois; Dr. Ramesh C. Pandey of Rutgers University, New Jersey; Prof. Koji Nakanishi of Columbia University, New York; and Prof. G. Ourisson of Universite Louis Pasteur De Strasburg, France.

Dr. Curt Enzell of Swedish Tobacco Company, Stockholm, Sweden; Prof. Franco Piozzi of University of Palermo, Italy; Prof. Jack Rowe of USDA, Madison, Wisconsin; and Prof. E. Fujita of Kyoto University, Uji, Kyoto, Japan, generously sent me valuable literature on their work on diterpenoids.

Renuka Mirsa

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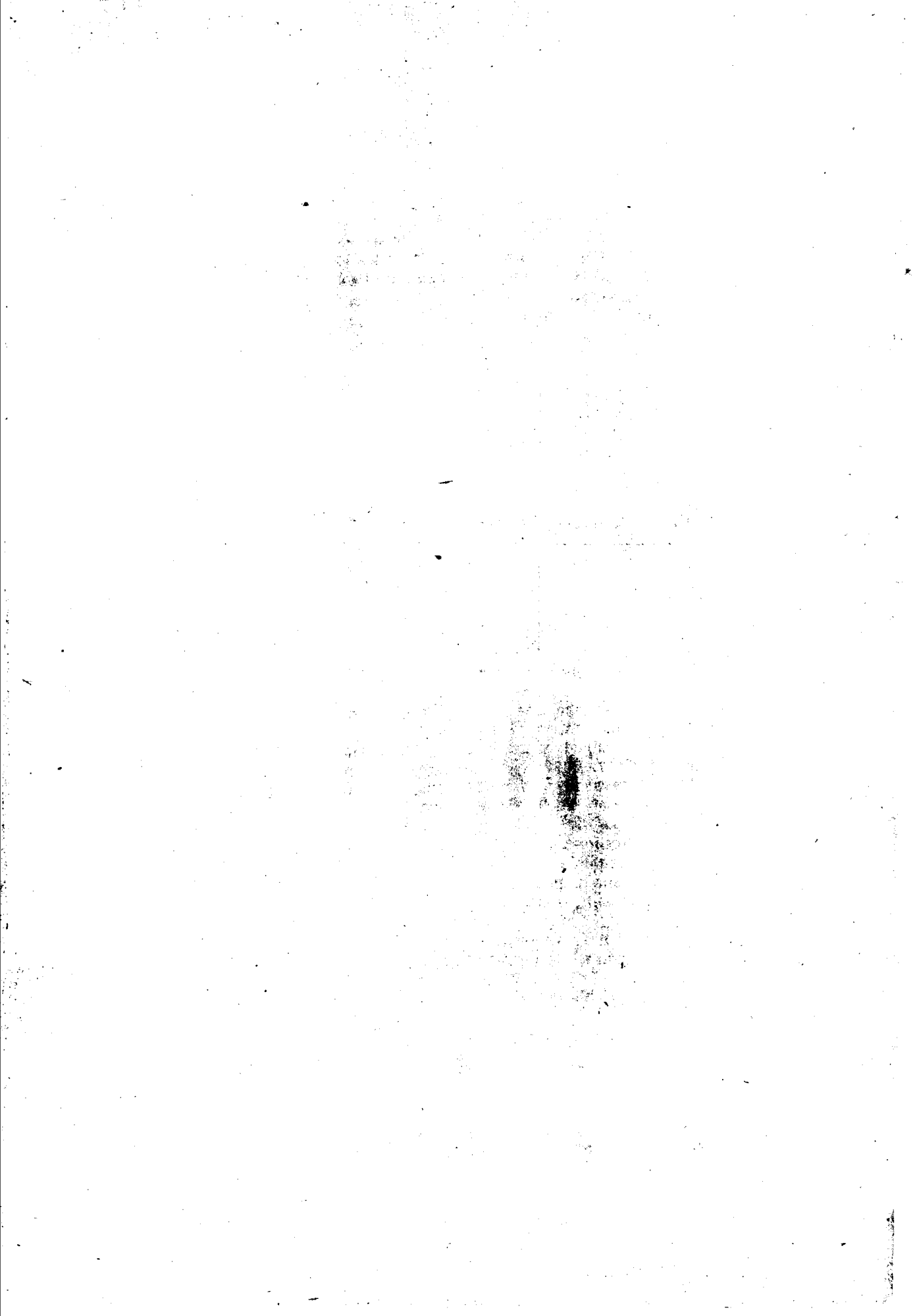
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*General Information and Skeletal-Type Index*





## GENERAL REMARKS ON THE USE OF THE BOOK

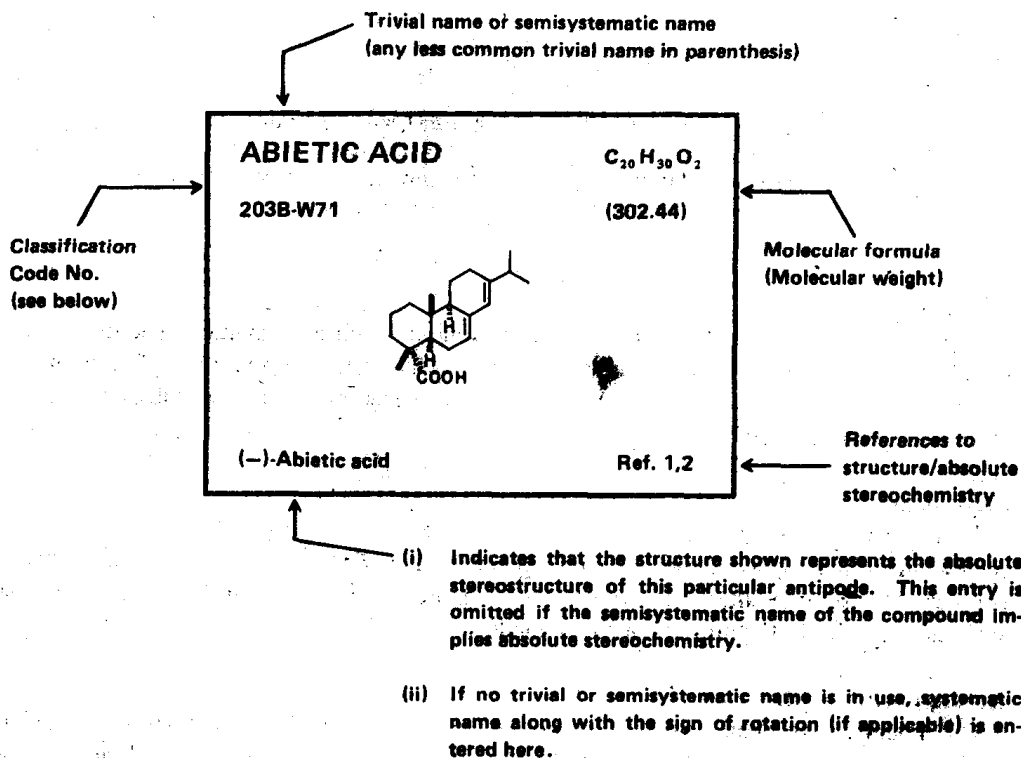
## Scope

As far as possible, all naturally occurring diterpenoids reported in literature until the end of December 1979 have been culled. These include 'nor' and 'homo' derivatives as well. Each compound has been assigned one page and the available information has been suitably summarized; optical antipode/racemate of the compound, if known to occur in nature, are also entered on the same page. In case, an alcohol and its simple derivatives such as esters, ethers, etc. occur in nature, the main entry is only for one of these compounds; however, a brief description of such derivatives is included on the same page or on additional following page(s).

## Format

The relevant information has been summarized on a suitable format, which is self-explanatory. However, some parts of the format require elaboration, so that the information given can be understood in proper perspective.

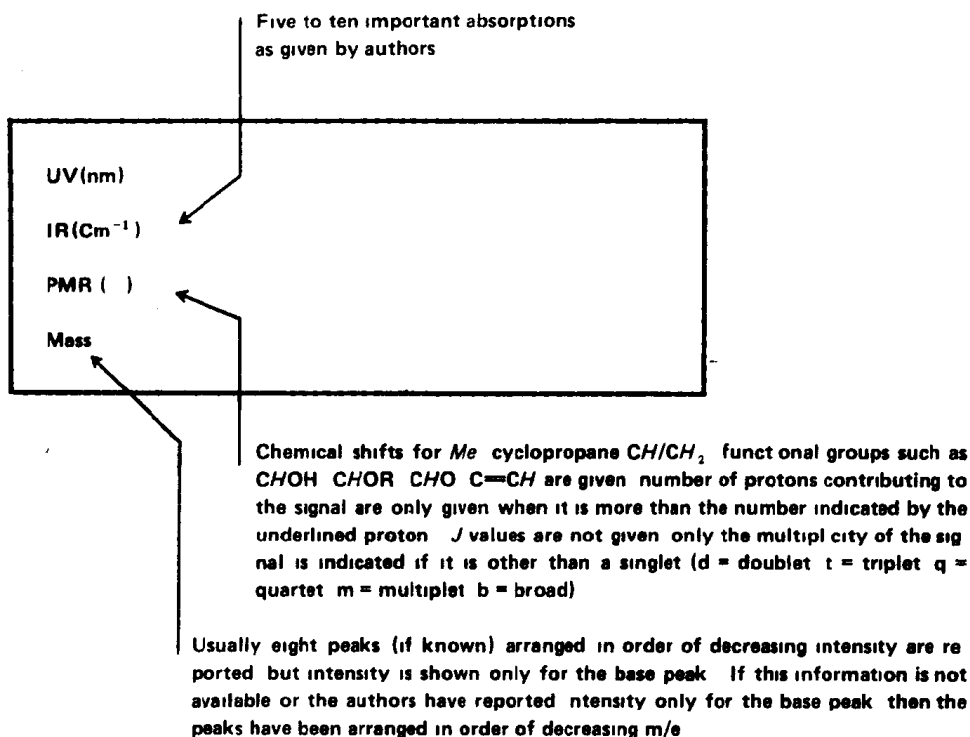
The upper-most left-hand section of the format carries the following information:



## Isolation/Occurrence

Usually the richest source for the compound is given along with its approximate percentage (if available) in the source. If both optical antipodes/racemic form occur in nature, then this information is summarized for each one of these. If any simple derivative of the compound occurs in nature, it is entered here.

Spectral data is summarized as under



#### Remarks

This section gives any additional known information such as a characteristic derivative, physical constants etc. of the naturally occurring derivatives reported under 'Isolation/Occurrence', reference to X-ray, <sup>13</sup>C-NMR spectra, synthesis, biosynthesis, biological activity or any other special remark.

#### References

Invariably the most pertinent references have been selected. In case, a suitable critical review on the topic is available, then a reference to the review rather than the original paper is given. In case of synthesis, if more than one report is available, then reference to the first synthesis and the last synthesis has been made.

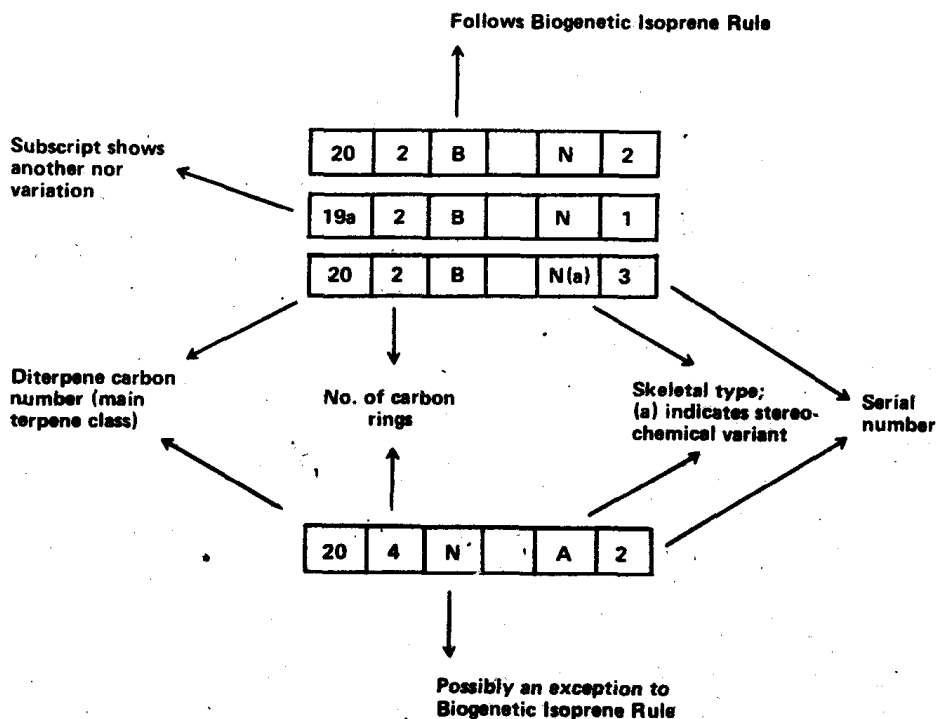
#### Arrangement of Material

Compounds have been classified as: *acyclic*, *monocarbocyclic*, *bicarbocyclic*, *tricarbo-cyclic*, *tetracarbo-cyclic*, and *pentacarbo-cyclic*. Within each of these broad categories, the compounds have been further classified on the basis of their carbon skeletons which have been arranged in terms of ring sizes, from smaller to larger. Within each skeletal type, the compounds have been arranged as: *saturated hydrocarbons*, *olefins*, *alcohols*, *aldehydes*, *ketones*, *acids (esters)*, *halogen derivatives*, *cyclic ethers/lactones*, *nitrogen* and *sulfur derivatives*. If more than one type of group is present in the molecule, then the compound is classified on the basis of the functional group of higher priority; for our purpose, functional group priority is considered to increase in going from saturated hydrocarbons to sulfur derivatives (see above). In each of these subgroups, further arrangement has been made on the following empirical basis; in order of increasing number of functional groups (for ex-

ample, double bonds/hydroxyls etc.), in order of (increasing) label number of the carbon atom carrying the functional group, in order of increasing size of the heterocyclic ring. Wherever applicable, further classification has been done on the following basis: compound with no prefix before isomer carrying prefix, *trans* before *cis*, *E* before *Z*, *erythro* before *threo*, *R* before *S*, less substituted olefin before more substituted, nonconjugated before conjugated.

### Classification Code No.

Each compound has a Classification Code No. which carries the following information: main terpene class, number of carbon rings, whether follows Biogenetic Isoprene Rule (B) or not (N), skeletal type and its serial number; skeletal types are designated by capital letters from A to Z, after which, if necessary, the designations continue as AX, BX etc. This is illustrated below:





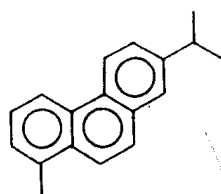
## GENERAL INTRODUCTION

Diterpenoids are, by definition,  $C_{20}$  compounds based on four isoprene ( $C_5H_8$ ) units. However, several naturally occurring compounds containing either fewer than 20 or more than 20 carbon atoms are, at present, known, and which have either a genetic or historical relationship with diterpenoids and hence, are best treated along with the related  $C_{20}$  compounds. The term diterpenoid, has come into considerable usage after 1955 and is now considered to be synonymous with diterpene and, is the preferred generic name for this class of natural products.

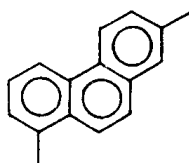
**Early development**

Diterpenoids to be first investigated were the resin acids, occurring in rosin (colophony), the steam-nonvolatile residue from the traditional manufacture of turpentine from the oleo-resinous exudate of trees belonging to the family *Pinacea*. These acids occur as rather complex mixtures of compounds of similar structure and hence their separation proved quite formidable. Thus, though a somewhat impure specimen of abietic acid, the most important constituent of rosin, had been obtained in 1824, it was not until 1910 that pure abietic acid was isolated.<sup>1</sup> By the close of the 19th century two more resin acids had been obtained pure: dextropimaric acid (1886)<sup>2</sup> and levopimaric acid (1887).<sup>3</sup>

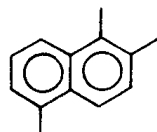
Though structural investigations on these acids started with the availability of even impure specimens of abietic acid and the pimaric acids, no real headway could be made until the introduction of the method of *dehydrogenation*.<sup>4</sup> As a matter of fact, the first application of the *dehydrogenation* method was made in the diterpenoid field, when in 1903 Vesterberg<sup>5</sup> subjected abietic acid to sulfur dehydrogenation and obtained retene, which several years later (1910)<sup>6</sup> was characterized as 1-methyl-7-isopropylphenanthrene (Structure 1). However, it was not until after 1921, when Ruzicka started systematic application<sup>4a</sup> of this method in his structural investigations on sesqui- and higher terpenes, that the full impact and potential of this powerful tool was revealed. The versatility of the method was further enhanced by the introduction of selenium<sup>7</sup> and platinum group metals<sup>8</sup> as reagents for dehydrogenation. The application of this method to the study of diterpenoids proved most basic for further development of diterpene chemistry. Thus, these investigations revealed that the tricyclic diterpenoids possess a perhydrophenanthrene skeleton and further belong to two distinct classes: those (abietic acid,<sup>5</sup> levopimaric acid<sup>9</sup>) giving retene (Structure 1), and those (dextropimaric acid<sup>10</sup>) generating pimanthrene (Structure 2) on dehydrogenation. Bicyclic diterpenes, such as sclareol<sup>11</sup> and agathenedicarboxylic acid,<sup>12</sup> under similar conditions, furnished agathalene (Structure 3), often accompanied by pimanthrene or 1,7,8-trimethylphenanthrene (Structure 4). These results coupled with the *isoprene rule*,<sup>13,14</sup> according to which terpene structures are formally divisible into "isoprene units", paved the way for arriving at the parent skeleton of these diterpenoids. Thus, formation of retene on dehydrogenation of abietic acid revealed the position of eighteen out of 20 carbon atoms of abietic acid and, the carbon skeleton could be extended to Structure 5 on the basis of isoprene rule, experimental confirmation of which could be had by 1933.<sup>15</sup> This vindication of isoprene rule led to its general acceptance as a good working hypothesis for exploring terpene structures. The position of two ethylenic linkages of abietic acid, as well as the site of the carboxyl function, which had been known to be tertiary in character, could be established by 1942, to reveal Structure 6 as the gross structure of abietic acid.<sup>16</sup>



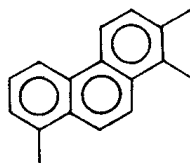
Structure 1



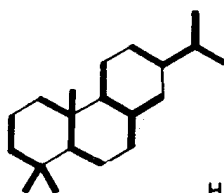
Structure 2



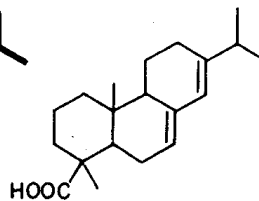
Structure 3



Structure 4

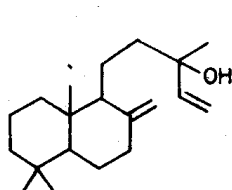


Structure 5

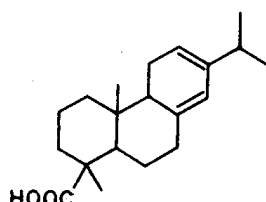


Structure 6

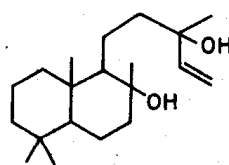
The evolution of this methodology was a remarkable achievement of Ruzicka's School and the period 1921 to 1950 saw the clarification of the gross structures of many of the then known cyclic diterpene acids and alcohols which had been obtained pure:<sup>17</sup> manool (Structure 7; 1936), le' opimarinic acid (Structure 8; 1940), sclareol (Structure 9; 1942), agathenedicarboxylic acid (Structure 10; 1943), dextropimaric acid (Structure 11; 1948), neoabietic acid (Structure 12; 1948). During the same period, structure of diterpene phytol (Structure 13), the alcoholic moiety of chlorophyll, and first discovered by Willstatter in 1907, was established;<sup>17</sup> again, isoprene rule played a valuable role in this effort.<sup>18</sup> The isoprene rule also aided structure elucidation of vitamin A, another diterpene alcohol, which was shown (1931) to be Structure 14 by Karrer's group.<sup>19</sup>



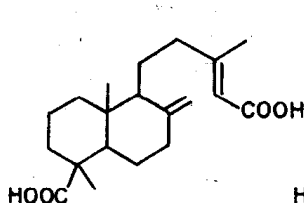
Structure 7



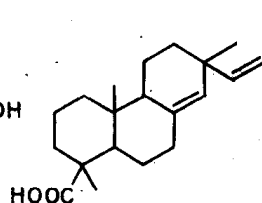
Structure 8



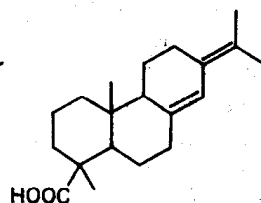
Structure 9



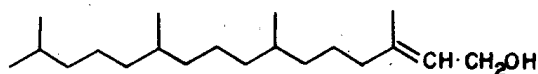
Structure 10



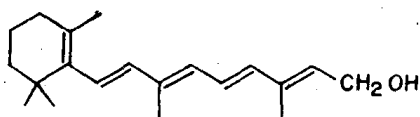
Structure 11



Structure 12



Structure 13



Structure 14

Once the gross structures of these diterpenoids had been established, workers directed their attention to stereochemical aspects. Barton<sup>17</sup> was able to deduce the relative configuration of abietic acid by 1949, while about the same time Ruzicka, Zwicky and Jeger<sup>20</sup> could ascertain the *trans* ring-fusion of the two rings in agathenedicarboxylic acid. On the basis of interrelationships, stereochemical assignments were also tentatively made<sup>17</sup> for other related compounds.

However, still by the close of 1950, there were several diterpenes<sup>17,21</sup> which either resisted further purification or proved too complex for structural analysis and had to await the development and introduction of more sophisticated methods of separation and structure determination.

### Present status

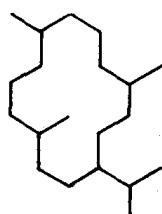
Around 1950 a new era in natural products chemistry can be considered to have begun. With the induction of newer and more effective separation techniques, and powerful spectroscopic methods of structural analysis (especially nuclear magnetic resonance), coupled with newer advances in organic chemistry theory and practice, our knowledge of the chemistry and biochemistry of naturally occurring molecules started accumulating at a rapid and often overwhelming rate. Another important factor which contributed in an important way to these advances was the role of biogenetic concepts. Specifically, in the area of terpenoids, the enunciation of *Biogenetic Isoprene Rule* (Ruzicka, 1953),<sup>14,18</sup> according to which terpene structures may be rationalized or preliminary structures deduced by accepted reaction mechanisms from hypothesized acyclic precursors such as geraniol, farnesol, geranylgeraniol, etc., proved vital.

The impact of the above developments is well-reflected in rapid advances in our knowledge of diterpenoids since 1950 and is best brought out by the following comparison. Simonsen's and Barton's classical work, *The Terpenes*, Volume III,<sup>1</sup> published in 1951 gives the final gross structures of only 17 diterpenoids belonging to some 8 skeletal types. By 1970<sup>22</sup> some 650 diterpenes falling into 70 skeletal types had been recorded and now this *Handbook* describes over 2000 diterpenoids embracing 176 skeletal types! Not only this, whereas the first absolute stereostructure of a chiral diterpene (abietic acid) was established only in 1953,<sup>23</sup> at present complete stereochemical details are available for a vast majority of diterpenoids. The various structural types known to date are discussed in some detail in a subsequent section. However, some highlights of these developments will be pointed out at this stage.

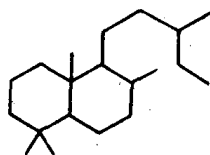
Of the over 170 carbon frame-works (see Skeletal-Type Index) known for diterpenoids at present, seven (Structures 15 to 21) of these account for some 50% of the known diterpenes, labdane (Structure 16) accounting for the largest number (320). Until recently, sesquiterpenoids were considered unique among the terpenoids in displaying skeletal and functional group versatility. Diterpenoids now have become equally diverse. Diterpenes of marine origin<sup>24</sup> have yielded a rich harvest of new carbon frame-works, especially higher isoprenologues of several well-known sesquiterpene types. Special mention may be made of:<sup>24</sup> xenicin (Structure 22; 1977) from Australian soft coral *Xenia elongata*, dilophol (Structure 23; 1976) from the Sicilian brown alga *Dilophus ligulatus*, dictyolene (Structure 24; 1977) from the Hawaiian brown alga *Dictyota acutoloba*, pachydictyol-A (Structure 25; 1973) from the Pacific seaweed *Pachydictyon coriaceum*, dilopholone (Structure 26; 1978) from



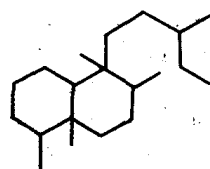
the brown alga *Dilophus prolificans*,<sup>25</sup> and xeniaphyllenol (Structure 27; 1978), a metabolite of soft coral *Xenia macrospiculata*.<sup>26</sup> Ginkgolides<sup>27</sup> (e.g. ginkgolide-A, Structure 28; 1967) from the root bark of the Japanese tree *Ginkgo biloba* L. represent a novel carbon framework having a *tert*-butyl group. Another unusual structure is that of pleuromutilin (Structure 29; 1962),<sup>28</sup> a metabolite of the fungus *Pleurotus mutilus*. However, undoubtedly, diisocyanoadociane (Structure 30; 1976)<sup>29</sup> from the Australian sponge of genus *Adocia*, and laurenene (Structure 31; 1978)<sup>30</sup> from the essential oil of *Dacrydium cupressinum*, represent some of the most bizarre diterpene structures. With a couple of exceptions, the structures so far mentioned were either arrived at by X-ray analysis or confirmed by this method. Of the unusual diterpene functionalities known to date, besides diisocyanide (Structure 30) already mentioned, the norditerpene sulfoxide (Structure 32, 1971),<sup>31</sup> the orthoester (Structure 33; 1975),<sup>32</sup> and the homoditerpene tetrahydrothiophene derivative, pharbitic acid (Structure 34; 1974) isolated<sup>33</sup> from the immature seeds of *Pharbitis nil*, may be cited. Several halogenated diterpenes, isolated from marine flora and fauna, are known at present.<sup>24</sup> The number of diterpene alkaloids, essentially tetra- and pentacarbocyclic, now runs into over 150.<sup>34,35</sup> Undoubtedly, the most important class of diterpenes discovered around 1940 and the most important biologically active diterpenoids are the gibberellins (Structure 20),<sup>36</sup> of which over 70 are known at present.



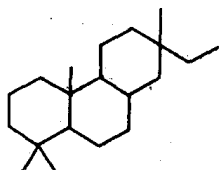
**Cembrene**  
Structure 15



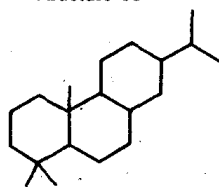
**Labdane**  
Structure 16



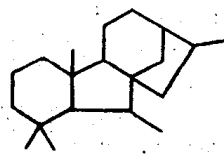
**Clerodane**  
Structure 17



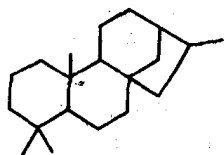
**Pimarane**  
Structure 18



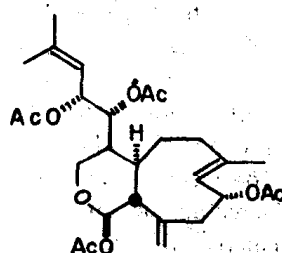
**Abietane**  
Structure 19



**Gibberellane**  
Structure 20



**Kaurane**  
Structure 21



**Xenicin**  
Structure 22