STUDIES IN NATURAL PRODUCTS CHEMISTRY

Vol. 7

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Studies in Natural Products Chemistry

Volume 7

Structure and Chemistry (Part A)

Edited by

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Structure and Chemistry (Part A)

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Vol. 1 Stereoselective Synthesis (Part A)
Vol. 2 Structure Elucidation (Part A)
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FOREWORD

The increasing interest in natural product chemistry is due to the wealth of novel structures being discovered from both terrestrial and marine plant materials, and their potential for application in medicine.

The present volume is the seventh of this series, and the third dealing with the structural aspects of natural products. It covers the chirality of natural products in relationship to their biological activity, enzyme-carbohydrate interactions, plant tissue culture as applied to the biosynthesis of terpenoids, and has chapters on oleanane triterpenes, bioactive constituents of mangrove plants and natural products from *Artemisia*. Other areas included are toxins from echinoderms, biosynthesis of carotenoids, bioactive compounds from Simaroubaceous plants and plants used in African traditional medicine. There is also a contribution on the chemistry of iridoids.

It is hoped that the present volume will be received with the same enthusiasm as the other preceding volumes of this series. I wish to thank Mr. Zahir Shah and Mr. Ejaz Soofi for their assistance in the preparation of the index, Miss Khurshid Zaman for editing and index preparation, Mr. Habib Alam and Mr. Asif Mahmood Raja for typing work and Mr. Mahmood Alam for secretarial help.

June 1990

Atta-ur-Rahman, Editor

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ERRATUM

In Volume 5, the former address of Professor Federico Arcamone was erroneously given. His present address is:

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Structure and Chemistry

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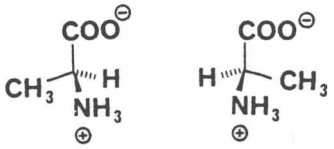
Chirality as Manifested in the Biological Activity of Natural Products

W. Gaffield

1. INTRODUCTION

The shape of natural forms has long fascinated man, in particular, their chirality or handedness (in the sense of 'right-handed and 'left-handed') (1). For example, examination of the chirality of the mouths of certain spiral shells or other marine structures discloses a relationship to habitat temperature (2). Thus, those with left dominant mouths predominate in colder regions such as the Arctic Circle whereas in warmer British waters spiral univalve shells display the opposite handedness with the mouth at the right (Fig. 1). Conversely, the direction of spiral (nutation) of climbing plants in the Northern and Southern hemispheres has been found to be unrelated to the apparent direction of motion of the sun (2). Chirality also appears macroscopically in quartz crystals, in which the crystal faces follow either a left-handed or right-handed sequence (3). (Fig. 2). Chirality is a geometric attribute with chiral objects being non-superimposable and achiral objects superimposable upon their mirror images (4). At the molecular level, chirality is exhibited by organic compounds such as L-alanine (1) and D-alanine (2) which bear a left-handed and right-handed sequence of groups attached to the central carbon atom, respectively, and at the particle level by an electron, whose left-handed or right-handed chirality is derived from the respective antiparallel, or parallel, relation between the linear momentum vector and the angular momentum axial vector (5, 6).



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A molecule is achiral when it possesses reflectional symmetry, i.e., any of the improper elements (center of symmetry, plane of symmetry, and an n-fold alternating axis of symmetry or rotation-reflection axis) (7). All chiral molecules are dissymmetric but they are not necessarily asymmetric,

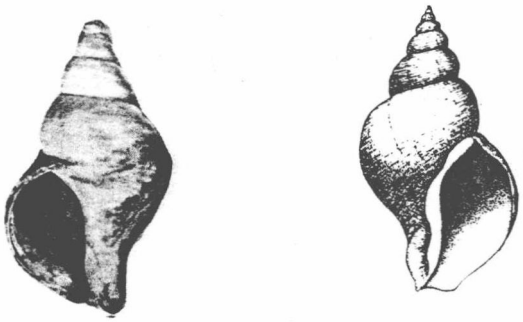


Fig. 1. Examples of handed spiral shells; Neptunia contraria (left), Neptunea antiqua (right). See, R. Gillard, Proc. Roy. Inst. Gt. Brit., 57 (1985) 1-18. (Courtesy of Professor R. D. Gillard, University of Wales, Cardiff). By permission of the Royal Society of Chemistry.

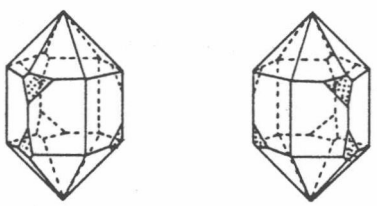


Fig. 2. Hemihedral left-handed (left) and right-handed (right) crystals of quartz.

i.e., lacking all symmetry elements except for the identity element, C_1 axis (8). Dissymmetric molecules may possess rotational symmetry and thus contain one or more simple axes of symmetry, C_n axes (4, 7). Implicit in the concept of achirality are two additional features. A conformational dependence of chirality may exist in certain compounds, such as n-butane and substituted biphenyls, but only in the latter is the activation barrier between the conformers high enough to permit stereoisomer separation under ambient conditions (9). Secondly, achiral molecules such as meso compounds may contain stereogenic centers (vide infra) (10).

Because chirality, like molecular mass, color or odor, is an inherent property of the entire molecule, the terms chirotopic and achirotopic have been advanced to describe chiral or achiral points (or segments),

respectively. Recent fundamental proposals (10) in stereochemistry have drawn a distinction between two separate and distinct features of molecules, their local geometry (symmetry) and their stereoisomerism. Often these two attributes have been combined into the single property of chirality. The new theory (10) has separated these two concepts into stereogenicity and chirotopicity which are uniquely linked properties. Stereogenicity, which is closely associated with the bonding arrangement of atoms, occurs when transposition of two bonded atoms or ligands produces a different stereoisomer, either an enantiomer or a diastereomer of the original molecule. Any atom that exhibits stereogenicity, such as the classical asymmetric carbon atom, is termed stereogenic or a stereocenter. Atoms that are not stereogenic but that reside in chiral environments, such as the methyl groups of steroids, are chirotopic (see also (11, 12)).

The first enantiomeric molecules were identified in 1848 by Louis Pasteur during his classic study of optical activity (13). Until Pasteur's research, chemists were puzzled by the discovery of optical isomers, substances which were alike in all respects except that one rotated plane polarized light to the right and the other to the left while a third form had no effect on polarized light and was therefore optically inactive. Pasteur obtained two similar sets of crystals upon recrystallization of racemic sodium ammonium tartrate which, similar to (+)- and (-)-quartz, were characterized by their hemihedral facets (Fig. 3). One set of crystals was isomorphous with crystals of (+)-sodium-ammonium tartrate, derived from (+)-tartaric acid deposited by maturing wines, and produced the same dextrorotation in solution. The other set had a non-superimposable mirror image form and, in solution, produced a negative specific rotation. The crystals of the sodium-ammonium salt of racemic tartaric acid also exhibited hemihedral

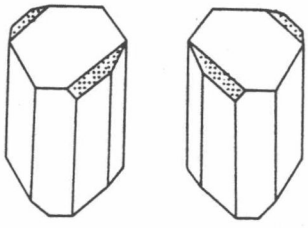
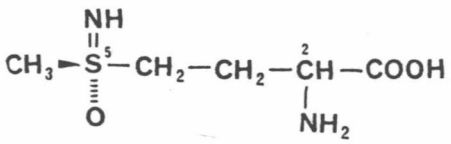


Fig. 3. Hemihedral crystals of dextrorotatory (left) and levorotatory (right) crystals of sodium-ammonium tartrate.

facets, but the hemihedry of some faced to the left and others to the right. Pasteur grasped the connection between the chirality of tartrate crystals and

their optical activity and extended these observations to the chirality of molecules (14). Molecular dissymmetry, as manifested by optical activity, was later claimed by Pasteur to provide a criterion to distinguish synthetic products produced in the laboratory from natural products derived from living organisms (15).

Most of the molecules involved in biochemical processes, indeed of all living organisms, are chiral. Usually only one of two enantiomeric forms such as L-amino acids and D-sugars occurs naturally in an organism, although plants or animals can also produce a mixture of enantiomers. Chiral recognition is now known to be one of the most fundamental principles of biological activity. Often only one of the optical isomers is responsible for a biological activity (e.g., (+)-estrone is the active estrogenic hormone and its enantiomer is inactive) while the other isomer is often inactive, or capable of causing unrelated side effects (e.g., thalidomide, vide infra.) One of the first examples which emphasized the importance of stereoselectivity was methionine sulfoximine, one of whose four diastereomers (specifically that of 2S,5S-configuration (3) (16)) potently inhibited glutamine synthetase and was responsible for the mammalian neurotoxicity ('canine-hysteria') (17) associated with the ingestion of nitrogen-trichloride bleached flour. Occasionally, enantiomers exhibit widely disparate properties. Thus, S-leucine (4) has a faintly bitter taste but the R-enantiomer is decidedly sweet (18). The odor of (+)-carvone (5) has been characterized as caraway-



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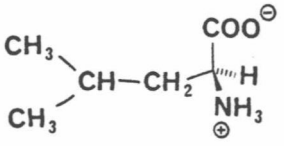

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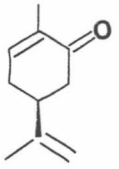
like, whereas the (-)-isomer possesses a spearmint-like aroma (19). A complicated relationship exists between chirality and pheromone activity; varied responses to enantiomers have been observed for different insects (20, 21). Certain insects respond to only one enantiomer of a pair, but others respond to both enantiomers equally or to specific ratios only. Sometimes the inactive antipode inhibits the action of the active enantiomer. Pheromonal specificity at the enantiomeric level is well-known as a principal isolation mechanism among sympatric species of Ips (22).

Two prominent natural products whose biological properties recently have been reexamined at the enantiomeric level are the active constituents of

catnip and Cannabis. (+)-Nepetalactone (6), whose structure represents a unique monoterpene, was isolated in 1941 and is responsible for the attractiveness of catnip to cats and lions (23). Apparently members of the Felidae do not show receptor site binding stereospecificity, because synthesis and biological evaluation of the unnatural antipode has revealed that both enantiomers of nepetalactone are equally attractive to mature cats, especially females (24). Cannabinoids of 3R,4R-configuration, which is the stereochemistry of natural delta-1-THC (tetrahydrocannabinol), have previously been claimed to exhibit relatively low stereospecificity in tests for psychotropic activity (25). Careful preparation and evaluation of enantiomerically pure 3R,4R- and 3S,4S-1,1-dimethylheptyl homologs of 7-hydroxy-delta-6-THC demonstrated that the 3R,4R-enantiomer (7) is one of the most psychotropic THC-type compounds known (26). The 3S-4S-enantiomer was



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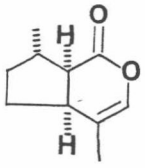

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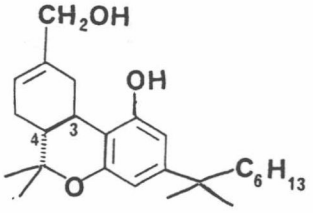

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devoid of psychotropic activity but instead possessed some analgetic and antiemetic activity (26). Any psychotropic activity reported earlier in the 3S,4S-series may have been due to the presence of small amounts of 3R,4R-enantiomer as a result of using only 95-98% enantiomerically pure α-pinene as chiral starting material (26).

Because it is now widely recognized that enantiomeric drugs, agrochemicals and natural products may show significant differences in their pharmacodynamic, pharmacokinetic and metabolic properties, a general awakening to the importance of absolute stereochemistry has occurred. A more complete knowledge of the structure and chemistry of a drug or environmental chemical will be demanded by the public in the future with a concomitant increase in the requirement of optically active compounds in both the pharmaceutical and chemical industries (27).

After a brief summary of the relevance of stereospecific activation and/or metabolism to the biological activity of two well-known compounds (benzo[a]pyrene and thalidomide), the relationship of stereochemistry to the toxic and teratogenic properties of several plant alkaloids will be described.