Chapter 1

THE ORIGIN AND THE NATURE OF NATURAL PRODUCTS

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1.1 INTRODUCTION

Throughout history, mankind has always been interested in naturally occurring compounds from prebiotic, microbial, plants and animals sources. Various extracts of flowers, plants and insects have been used for isolating compounds whose task, color and odor could be used for various purposes. Many natural products, such as plant hormones, have a regulatory role, while others function as chemical defense against pests. The role of certain compounds is to act as chemical messengers, such as sex-attractants (pheromones) in insects, terrestrial and marine animals and humans. What is the origin of natural products?

It has been suggested that earth planet was created about 5000 million years ago and human beings were created about 100 000 years ago. In the beginning, God created the heaven and the earth. And God said: Let the earth put forth grass, herb yielding seed, and fruit tree bearing fruit after its kind, and God saw that it was good. And there was evening and there was morning on the third day. On the fifth day, he created the fish in the sea and the fowl in the air. In a sense, we are concerned with the third and the fifth days in this review. There are other ways in which the idea of creation has been represented. Recently, there has been a literary expression

SELECTED TOPICS IN THE CHEMISTRY OF NATURAL PRODUCTS

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of Thornton Wilder in his book, *The Eighth Day*, "Nature never sleeps. The process of life never stands still. The Bible says that God created man in the sixth day and rested, but each one of these days was many millions of years long (Fig. 1)."[1]

1.2 HUMAN MEDICINAL AGENTS FROM PLANTS

The ancient Egyptians have described several useful preparations such as opium and castor oil. They also used "rotten bread" for treating infections which "resembles" our use of antibiotics produced by moulds and fungi. The Roman physician, Dioscorides, studied the medical uses of hundreds of plants and wrote the first systematic *materia medica* during the first century. He also described the medicinal properties of wines.

The Chinese are considered as leaders in using natural products for healing. The oldest compilation of Chinese herbs is Shen Nung Pen Ts'ao, which lists 385 materials. Pen Ts'ao Ma catalogue, written by Li-Chen during the Ming Dynasty, (1573–1620) mentions 1898 herbal drugs and 8160 prescriptions.

5267 medicinal herbs were used in China in 1979. One of the most famous herbs among them is the ginseng root, *Panax ginseng* used for health maintenance and the treatment of various diseases. Another popular folk drug is the extract of the Ginkgo tree, *Ginkgo biloba*, which can improve memory and sharpen mental alertness.

During the 17th century, the Jesuits brought with them from South America the bark of the China tree for the treatment of malaria. In 1820, Pelletia and Caventou isolated from the China tree the active compound, quinine. American Indians used the powerful hallucinogen, mescaline, for a long period. The Indian hemp plant, *Cannabis sativa*, has been used since 3000 BC, and it is also used as marijuana or hashish. Its constituent, Δ^1-THC (tetrahydrocannabinol) is responsible for its mind-altering effect. It was synthesized by Mechoulam and Gaoni.[2]

The rapid and impressive development of organic chemistry in the 19th century had a tremendous effect on the discoveries of natural products. Towards the end of the 19th century, microbiology has developed enormously. The antibiotic penicillin was first isolated by Alexander Fleming

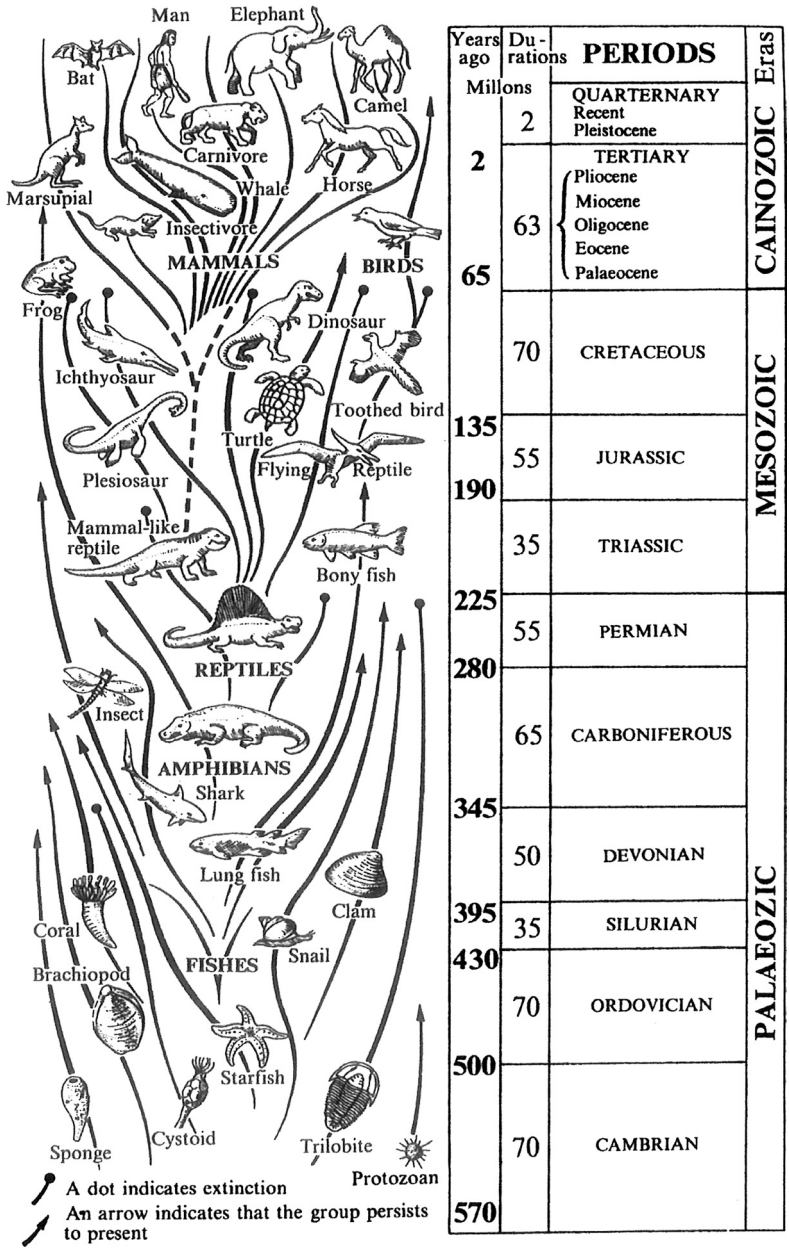


Fig. 1. The palaeontological record of the Palaeozoic.[1]

in 1929. In 1944, Waxman isolated streptomycin which is used for the treatment of tuberculosis.

1.3 RECENT PROGRESS IN THE CHEMISTRY OF NATURAL PRODUCTS[3,4,5]

Among the recent outstanding contributions to the chemistry of natural products is the conformational analysis designed by Derek Barton. He used it for the structural determinations of many complex molecules such as β-amyrin and cycloartenol. Robert B. Woodward was involved in the structural determinations of penicillin, strychnine, patalin, terramycin, aureomycin and the synthesis of Vitamin B12.

The other important scientists include V. Prelog, L. Ruzicka, P. Plattner, O. Jeger, A. Eschenmoser, D. Arigoni, A. Dreiding, J. Dunitz and many more. Other famous investigators regarding the biosynthetic studies were A. Birch and R. Robinson who studied the biosynthesis of polyketides having C_6-C_3-C_6 backbones such as plant phenolics, polyene macrolides, terpenoids and alkaloids, sterols, fatty acids and prostaglandins (discovered in seminal fluids).

Otto Wallach (1847–1931) proposed the "isoprene rule" and many scientists were engaged in isoprenoid studies. Among them was Wieland, Windaus, Karrer, Kuhn, Butenandt and Ruzicka. Paul Karrer (1889–1971) established the foundation of carotenoid chemistry which was proceeded by Otto Isler and Hans Eugster. Adolf Butenandt (1903–1998) dealt with human sex hormones and obtained estrone from pregnant women, progesterone from sow ovaries and 50 mg of androsterone from 400 gallons of male urine. Together with Peter Karlson, he isolated 25 mg of ecdysone (insect and crustacean molting hormone) from 500 kg of silkworm larvae.

Studies on isolation from adrenal cortex and the synthesis of cortisone (in 28 steps), an anti-arthritic hormone, was accomplished in the 1940s by Woodward and others. Cortisone was used as an important military medicine during World War II. Carl Djerassi from Stanford University directed the research at the Syntex Laboratories, which led to the synthesis of the first oral contraceptive "pill" for women. Koji Mori is very active in the field of the synthesis of pheromones.

Extracts of toxic plants has been used for hunting and murder throughout the world for thousands of years. Thus, *Strychnos* and *Chondrodendion* (both containing strychnine) were used in arrow poisons. The Colombian arrow poison consists of toxins from the legs of frogs. When rye is infected by the fungus, *Claviceps porpurea*, the toxin ergotamine and a number of ergot alkaloids are produced. These compounds cause serious illnesses.

In 1952, Bloch and Woodward suggested a mechanism for the cyclization of squalene to cholesterol. In 1962, Francis Crick and James Watson described the double helix structure of proteins. Hodgkin determined the structure of vitamin B12 and of penicillin through collaboration between Woodward and Eschenmoser, involving postdoctoral fellows. In 1877, Alexander Fleming discovered penicillin which was active against tuberculosis.

The study of marine natural products has great possibilities for new products. Thus, Paul Scheuer from Hawaii studied bioactive compounds from mollusks and other marine sources. Luigi Minale, Raffaele Riccio and Maria Iorizzi from Italy, conducted a comprehensive research on marine steroidal glycosides. Joel Kashman from Tel-Aviv University investigated on the biologically active natural products from marine organisms.

Palytoxin, a most poisonous substance from the Hawaiian soft coral, *Palythoa toxica*, was isolated by Woodward. It contains about 64 chiral centers and seven double bonds, capable of E/Z isomerism, giving rise to the possibility of 2^{71} isomers (close to Avogadro's number). It was synthesized by Armstrong, *et al.*, in 1989. In 1996, a most toxic toxin, maitotoxin was isolated and its structures was determined by two Japanese groups. Its empirical formula is $C_{164}H_{256}O_{68}S_2NO_2$ and its molecular weight is 3422. Human medicinal agents from plants were described by Kinghorn and Balandrin.[6]

1.4 THE CLASSIFICATION OF NATURAL PRODUCTS

The classification of natural products may follow the four schemes below:

(1) Classification based on the molecular skeletal structure: Open-chain aliphatic, alicyclic and cycloaparaffinic, aromatic, benzenoid and heterocyclic.

(2) Classification based on physiological activity: The interest in natural products is frequently initiated by attempts to isolate and clarify a physiologically active principle of plant or animal origin. Actually, many medicines currently in use are natural products, e.g. alkaloids, such as morphine and penicillin G.
(3) Classification based on chemotaxonomy: The field of chemotaxonomy attempts to review plant constituents according to plant taxa. Namely, constituents are regarded as markers for evolution as well as the classification of plants.
(4) Classification based on biogenesis: It has been established that the primary synthetic process in nature is photosynthesis by which green plants utilize the energy of the sun for the production of organic compounds from carbon dioxide. The initial products of photosynthesis are carbohydrates. Further metabolic alterations lead to the formation of a pool of organic compounds of low molecular weight and simple structures such as carboxylic- and amino acids, which are vital for the living organisms. They form the synthetic starting materials for specific, genetically controlled, enzymatically catalyzed reactions that lead to the complex compounds that characterize the secondary metabolism of plants and mammals. The reaction pathway leading to a particular natural product is called the biosynthetic pathway and the corresponding event is known as biogenesis. Different plant and animal species can employ different biosynthetic pathways to produce the same metabolite. This feature can be employed in the classification of plants in terms of their chemotaxonomy.

Of the four major classes of biochemicals (carbohydrates, proteins, nucleic acids and lipids), experiments have shown that the first three classes could have arisen through prebiotic chemistry.[7] Although the biosynthesis of many natural products can be traced back to acetate (e.g. fatty acids, terpenes and polyketide biosynthesis) or amino acids (e.g. alkaloid biosynthesis), there are many whose biosynthetic origins are either obscure or result from a complex combination of pathways (Fig. 2).

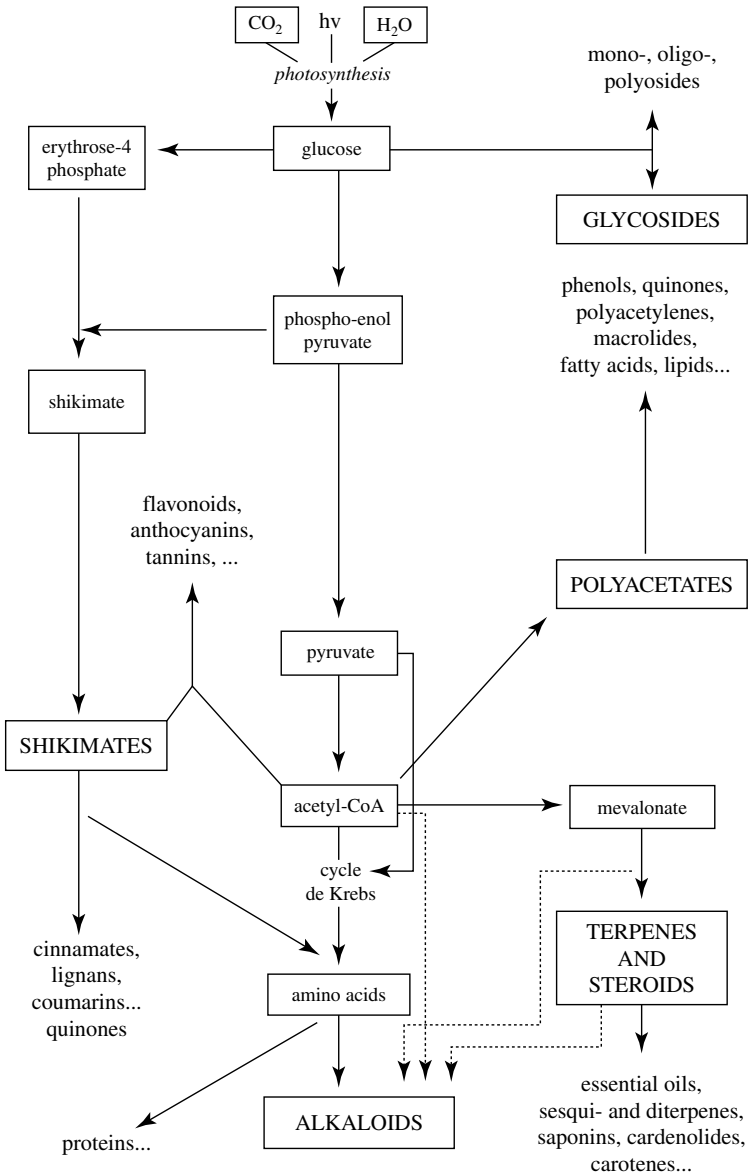
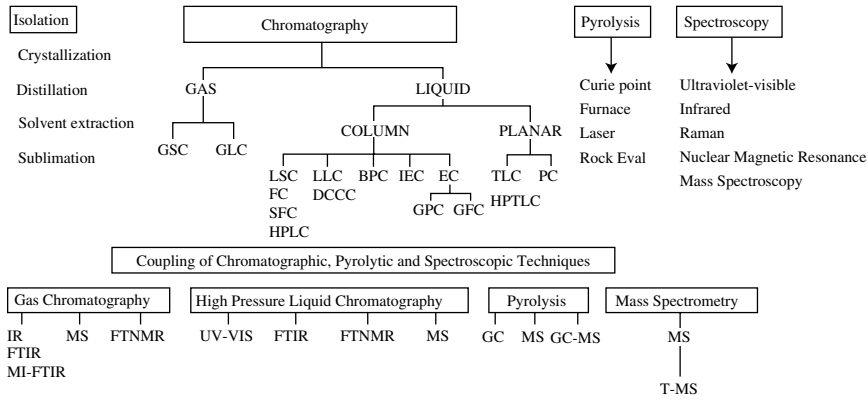


Fig. 2. Schematic presentation of natural products formation.[8]



Chromatographic and spectroscopic techniques for detection and identification of organic compounds.

GC, gas chromatography; GLC, gas–liquid chromatography; GSC, gas–solid chromatography; TLC, thin layer chromatography; HPTLC, high performance thin layer chromatography; PC, paper chromatography; LSC, liquid–solid chromatography; FC, flash chromatography; SFC, supercritical fluid chromatography; LLC, liquid–liquid chromatography; DCCC, droplet counter current chromatography; PBC, bonded phase chromatography; HPLC, high pressure liquid chromatography; IEC, ion exchange chromatography; EC, exclusion chromatography; GPC, gel permeation chromatography; GFC, gel filtration chromatography; IR, infrared; UV, ultraviolet; NMR, nuclear magnetic resonance; MS, mass spectroscopy; FT, fourier transform; T-MS, Tandem mass spectroscopy; MI-FTIR, matrix isolation fourier transform infrared.

Fig. 3. Chromatographic and spectroscopic techniques.[9]

1.5 IDENTIFICATION OF NATURAL PRODUCTS BY CHROMATOGRAPHIC AND SPECTROSCOPIC METHODS

Recently, natural products chemistry has undergone explosive growth due to advances in isolation techniques, synthetic and biosynthetic approaches as well as spectroscopic and chromatographic methods.

The advent of computers and Fourier transform completely revolutionized the detection and identification of organic compounds. Modern automated instruments allow very small samples in the nanogram (10^{-9} g) range to be characterized in a very short time. The application of Fourier transform nuclear magnetic resonance (FTNMR) and Fourier transform infrared (FTIR) allows recovery of the sample in contrast to mass spectrometric (MS) determination which is a destructive but quite often a necessary technique.

Modern methods used to separate complex organic mixtures utilizing gas-liquid chromatography (GLC), high-pressure liquid chromatography (HPLC), and droplet counter-current (DCC) chromatography can separate samples rapidly and efficiently in the picogram range. This has been impossible until recently. Coupling the chromatographic instruments to spectrometers enables a partially automated analysis in an even shorter period of time. The following coupling of chromatographic instruments has been performed: GC-MS, GC-FTIR, GC-MI-FTIR, GC-UV-VIS, HPLC-MS, HPLC-FTIR, HPLC-FTNMR and MS-MS (Fig. 3).

These semiautomated systems of analyzing and characterizing small samples are vital to the natural product organic chemist and biochemist for the detection of highly active substances in extremely low concentrations in living organisms. A typical example is in the field of pheromones which includes insect sex attractants that differ quite markedly in many insects. Their concentration has often been found in the 10^{-9}–10^{-12} g range.

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