Synthesis of Urea

--Total Synthesis of Natural Products, the Opportunities and Challenges Given to Chemists by Nature

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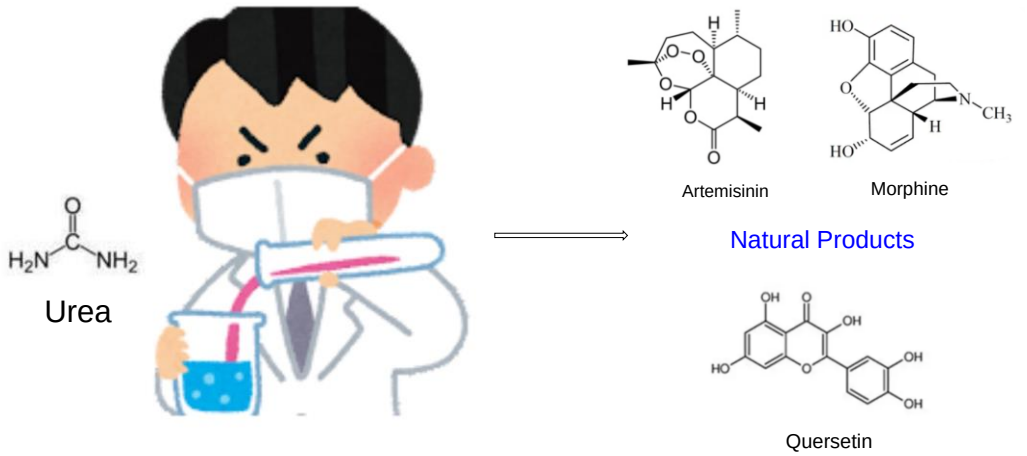

Urea, also known as the carbamide, is a compound that is widely recognized and utilized. It finds applications as a fertilizer and is even incorporated into various medical products, such as urea cream. As the name suggests, urea is a constituent of urine, which in the past could only be obtained through repetitive purification and extraction from animal urine. Notably, urea holds the distinction of being the first organic substance synthesized from inorganic precursors. Let me tell you the story of the human synthesizing urea, and the history of organic synthesis of natural products.

During the late 18th and early 19th centuries, a clear distinction between "inorganic" and "organic" substances was emerging. At that time, a prevalent belief in the field of chemistry was that organic matter was exclusively derived from living organisms, such as plants and animals, through a unique life force or "vitality." Chemical laboratories were thought to have the ability to synthesize inorganic compounds but could only convert organic compounds into different organic compounds, lacking the capability to

produce organic matter from inorganic sources. It was widely accepted that organic substances, which were believed to possess this inherent life force, could not be created synthetically from inorganic substances. This perspective persisted for a considerable period, until the synthesis of urea shattered this notion.

The pioneering chemist responsible for the synthesis of urea was the German scientist Friedrich Wöhler. In 1824, Wöhler attempted to prepare ammonium cyanate ($[NH_4]^+[OCN]^-$) using a simple method - combining cyanic acid and ammonia. However, he unexpectedly synthesized a white crystalline substance. Wöhler also discovered that treating silver cyanate or lead cyanate with ammonium chloride solution and heating it could also produce this type of crystalline substance. The solid crystals obtained through these three methods were identical. Furthermore, according to a series of experiments, this compound was not the expected ammonium cyanate. So, what exactly is this white crystalline substance? Wöhler compared the white crystalline substance he synthesized with the urea extracted from urine and found that they were the same substance. Urea belonged to organic compounds, and yet he had synthesized it using inorganic substances, namely cyanic acid and ammonia! This is a great discovery for human first synthesizing organic product from inorganic starting materials. [1]

What does Wöhler's groundbreaking accomplishment means? It directly challenged the prevailing "vitality theory" of the time, which claimed that only living organisms could produce organic compounds. By successfully synthesizing urea, Wöhler effectively demonstrated that organic substances could be created artificially from inorganic precursors, thus paving the way for further advancements in the organic total synthesis of natural products. Do you know what are the “natural products”? In nature, organisms engage in diverse forms of information exchange, with chemical release and reception being one of the most prevalent mechanisms. Insects and other organisms, for instance, communicate through the secretion of pheromones. Consequently, we refer to organic chemical substances that possess physiological or biological activity and are

produced by organisms themselves as natural products.

What challenges and opportunities do “natural products” give to us humans? Because of extensive natural selection and optimization by organisms, natural products often possess unique structures and the ability to selectively bind to specific targets. Some of these natural products can be directly utilized in disease treatment. For instance, artemisinin, which was extracted by Chinese scientists from the traditional Chinese medicine Artemisia annua in 1972, has proven to be a highly effective drug for combating malaria. Its discovery has provided a formidable weapon in the battle against malaria, leading to the salvation of countless lives. However, such natural products are often scarce and challenging to obtain by extracting from organisms.[2] By developing organic synthesis methods for natural products, we can obtain these substances in substantial quantities and with high efficiency, thus harnessing their potential in various fields. Since the initial isolation of natural products from nature, scientists have been tirelessly exploring new methods to artificially synthesize them, progressing from simple to complex molecules. This journey has encompassed various approaches, such as semi-synthesis, total synthesis, biosynthesis, and genetic recombination of natural products. Over time, scientists have made significant strides in the field of natural product synthesis. Initially, attempts at total synthesis faced numerous challenges and often resulted in failures. However, these setbacks served as valuable learning experiences, driving advancements in the field of organic chemistry. Scientists persevered and used these failures as steppingstones towards refining their techniques and understanding the intricacies of natural product synthesis.

With each endeavor, scientists gained deeper insights into the synthesis of natural products, paving the way for further advancements in the field. This relentless pursuit of knowledge has not only expanded our understanding of organic chemistry but has also unlocked the potential for artificially synthesizing a wide range of natural products.

References:

[1] *Nomenclature of Organic Chemistry : IUPAC Recommendations and Preferred Names 2013 (Blue Book)*. Cambridge: The Royal Society of Chemistry. 2014. pp. 416, 860–861. doi:10.1039/9781849733069-FP001. ISBN 978-0-85404-182-4. The compound H_2N-CO-NH_2 has the retained named 'urea', which is the preferred IUPAC name, (…). The systematic name is 'carbonyl diamide'.

[2] Chunyin Zhu, Silas P.Cook, A Concise Synthesis of (+)-Artemisinin. J. *Am. Chem. Soc.* **2012**, 134, 33, 13577-13579

Methods and Acknowledgement

I have written this entire essay using DeepL and Grammarly software. DeepL was used for translation and Grammerly was used for checking words spelling and grammar mistakes.

I also thank Dr. Mark Vagins and Shota Saito for their helpful suggestion for this essay.