Rotenone- Discovery, Synthesis, and Applications

Huraiya Adhora

Dr. David P. Brown

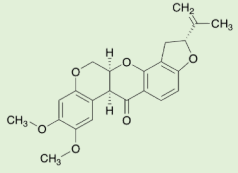
Abstract

Rotenone is a crystalline compound that belongs to the rotenoid family. Rotenoids are naturally occurring substances that contain a cis-fused tetrahydrochromeno[3,4-b]chromene nucleus. This colorless and odorless compound has insecticidal, acaricidal, and pesticidal properties. Rotenone has gained popularity in fish management. The natural compound works by inhibiting complex I of the mitochondrial respiratory chain, leading to oxidative phosphorylation, limited ATP synthesis, and the formation of reactive oxygen species. The focus of this research is to explore the discovery, synthesis, current and future application of Rotenone.

Discovery

Rotenone is a naturally occurring compound that is mainly derived from the roots and stems of Derris elliptica, a species of leguminous that was found in Africa, Central America, southeast Asia, and the southwest Pacific Islands. The earliest recorded use of rotenoids as an effective insecticide was recorded in 1848; rotenoids were used as a means to limit leaf-eating caterpillars. However, rotenone itself was not isolated until 1895 by Emmanuel Geoffroy. Geoffroy named the chemical compound nicouline and isolated it from the planet Robinia nicou, now known as Lonchocarpus nicou. In 1902, a Japanese chemist, Kazuo Nagai isolated the roots of Derris and called it rotenone. "Roh-ten" is the Japanese word for the plant and "one" indicates that the compound is a ketone.

Structure



Properties

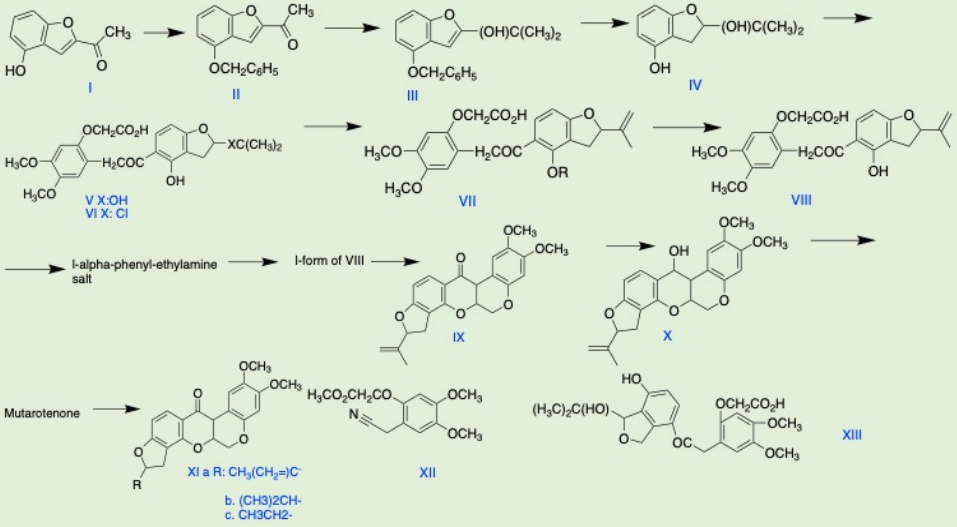
Appearance: Colorless and brownish crystal or a white to brownish-white crystalline powder
Chemical Formula: $C_{23}H_{22}O_6$
Molar Mass: 394.4 g/mol
Odor: Odorless
Taste: Tasteless
Boiling Point: 410°F
Melting Point: 330°F
Solubility: Soluble in organic solvents such as ethanol, DMSO, and chloroform

Initial Uses

Rotenone has been registered as a pesticide in the United States under the Federal Insecticide Fungicide Rodenticide Act since 1947. Rotenone has lethal effects on insects; however, it is essentially harmless to humans and other warm-blooded vertebrates. Rotenone is a valuable fish management tool and allows fisheries to restrict unwanted fish, reduce toxic and harmful fish, and protect and restore threatened species. However, its use has recently been criticized. The use of rotenone in water has been questioned by environmental and animal rights groups throughout the United States. In response to increased attention to proper rotenone use, the U.S. Fish and Wildlife Services in partnership with the American Fisheries Society released a Rotenone SOP Manual. The manual provides fishery managers with procedures needed for carrying out projects with rotenone in a way that is safe and effective.

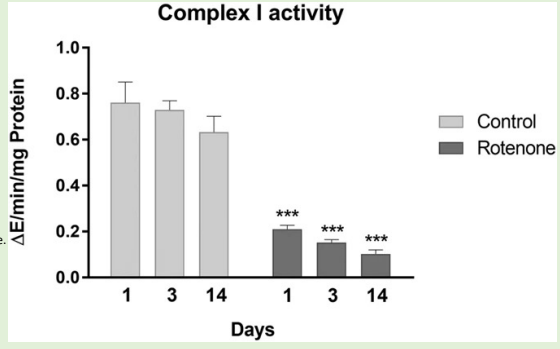
Initial Synthesis

The first formal synthesis of rotenone was carried out by Masateru Miyano, Akio Kobayashi, and Masanao Matsui at Tokyo University of Agriculture and Technology. The group reported the total synthesis of natural l-rotenone in 11 steps from commercially available resorcinol. Compound IV proceeded through a Hoesch reaction, a form of Friedel-Crafts acylation with hydrogen chloride and a Lewis acid catalyst. The Hoesch reaction accompanied by saponification presented a mixture of dl-hydroxydihydroderrisic acid (V), dl-chlorodihydrogerrisic acid (VI), and an isomer (XIII) of V. Dl-hydroxydihydroderrisic acid (V) was the main product, however, only compound XIII could be isolated. The remaining two groups were separated via chromatography. An IR spectrum taken of the synthesized dl-VIII in chloroform was identical to that of l-derrisic acid and it was concluded that the synthetic sample of derrisic acid in this experiment was racemic. The l-derrisic acid was cyclized to dehydrorotenone (IX) with acetic anhydride in the presence of sodium acetate. The resulting product was then converted to rotenol (X) by sodium borohydride in warm dioxane. Compound X went through a process known as Oppenauer oxidation. In the final step, mutarotenone can go through thermal isomerization and be converted to rotenone. In the first formal synthesis of Rotenone. The yield of dl-derrisic acid, the immediate precursor of rotenone, was approximately 0.01%.



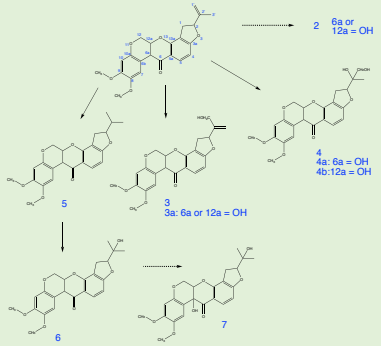
Mechanisms of Toxicity

According to the World Health Organization, rotenone is moderately toxic to humans. Human exposure mainly occurs through its extraction and formulation as a pesticide and piscicide.
Rotenone, however, is highly toxic for aquatic life.
Exposure is expected for the handlers as well as those in close proximity to the body of water.
Rotenone has a greater potential for toxicity when used as a piscicide as the compound is stable in water for up to 6 months.
Rotenone works by inhibiting complex I (ubiquinone oxidoreductase) of the mitochondrial respiratory chain (MRC).
This inhibition leads to diminished oxidative phosphorylation with limited ATP synthesis. Complex I is the first enzyme of the respiratory chain and oxidizes NADH generated in the Krebs cycle.
The complex uses two electrons to reduce ubiquinone to ubiquinol.
The mechanism of action (MOA) consists of the repression of electron transfer from the iron-sulfur cents in complex I to ubiquinone.
Additionally, incomplete electron transfer can lead to the formation of reactive oxygen species (ROS).
Rotenone-induced ROS production can cause damage to mitochondrial components such as DNA and sequentially lead to apoptosis



Biodegradation

Various species of Abdidia, Aspergillus, Cunninghamella, Trichothecium, Penicillium, and Phanerochaetewere can transform rotenone to one or more metabolites. Among the microorganisms that had the abilities to transform rotenone (1) , it was found that Cunninghamella blakesleeana produced consistently higher yields of metabolites.



Parkinson's Disease

In 2002 Greenamyre et al. investigated the relationship between rotenone exposure and the potential of developing Parkinson's. The researchers observed the selective degradation of the dopamine neurons in the substantia nigra resulting from the repression of complex I. Degradation started in the nerve terminals and progressed through the cell bodies, the observed pathology matched that seen in PD. From a behavioral perspective, rats exposed to rotenone developed symptoms of Parkinson's such as bradykinesia and rigidity. The results collected confirm that a defect in complex I can cause Parkinson's. The work completed lays the foundation for further research in finding the link between rotenone and PD.

Anticancer Activity

Work completed by Hu et al. in 2016, suggests that the activation of membrane subunit NOX2 and subsequent release of reactive oxygen species is responsible for rotenones anticancer activity. The investigators reported that exposure to rotenone induces mild NOX2-dependent oxidative stress, this results in impaired autophagic flux leading to accumulation of LC3 and p62/STSQM1. The induction occurs through the PI3K/Akt/mTOR signaling pathway. Furthermore, the investigators reported that chronic exposure to rotenone increase NOX2-dependent oxidative stress and worsens the autophagic machinery and decreases p62 levels as a result of increases autophagic flux. The study suggests that rotenone is potentially useful in chemotherapeutic and anticancer treatments. The goal of ongoing investigations at St. John's University is to develop a novel approach to synthesizing rotenone derivates which will be studied as a new chemotherapeutic agent.

References

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