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HETEROCYCLES IN FOCUS

Biological activity and synthesis of 5,6-dihydroxyindole-2-carboxylic acid – biosynthetic precursor of melanins (microreview)

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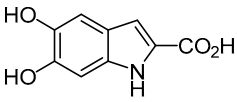

The microreview considers the biological activity and methods of obtaining natural melanin pigments and their biosynthetic precursor 5,6-dihydroxyindole-2-carboxylic acid. The key methods for the synthesis of 5,6-dihydroxyindole-2-carboxylic acid, published over the past 8 years (2012–2020), are presented.

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The properties and uses of melanins

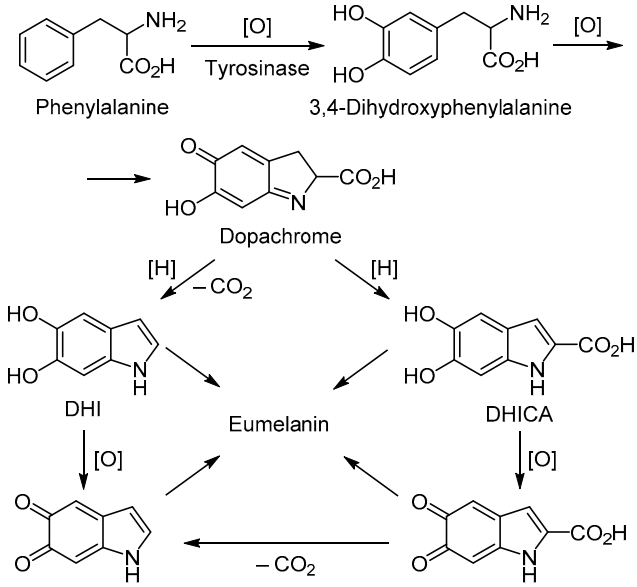
It is known that melanins, natural pigments contained in the human body, are capable of protecting living tissues from UV radiation.[1] On the basis of plant melanins, preparations have been created and patented that have antiviral activity against influenza viruses, herpes simplex virus type 2, HIV-1, and vaccinia virus.[2] In addition, earlier in the USSR, melanin-containing immunomodulators, such as Befungin, were developed to fight cancer, including in patients with stage IV cancer.[3]

Compared with known drugs, natural melanins have a number of advantages as therapeutic agents: a broad spectrum of action, a variety of useful biological activities, low toxicity. However, they also have a number of disadvantages, first of all, the complex process of isolation, as well as the limited solubility in H_2O of the pigments themselves and, as a result, low bioavailability. Since melanins are carboxy-containing biopolymers, they must be converted to an anionic form which is better soluble in H_2O. Difficulties also arise with the purification of natural melanins. In living organisms, they are present in the form of complexes with proteins from which they must be separated. The thorough cleaning process requires dialysis using large amounts of deionized H_2O which increases the cost of the final product.[4]

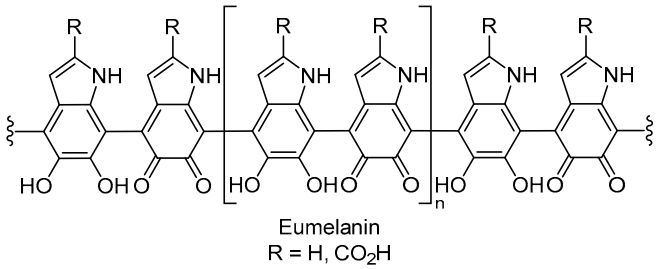
In turn, the biosynthesis of melanin in mammals begins with phenylalanine which enters the body with food and involves successive stages of oxidation with the participation of enzymes and endogenous H_2O_2.

At the last stages of melanin biosynthesis, 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid

The properties and uses of melanins (continued)



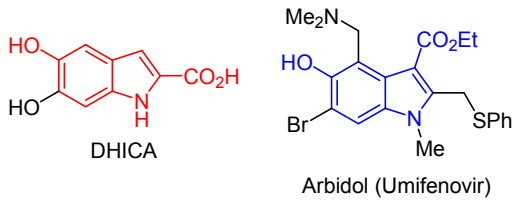
(DHICA) are present, the oxidative combination of which leads to natural eumelanin.[1]



Currently, natural precursors – small molecules from which the body builds its active melanin defense, for example, DHICA – attract the attention of researchers.

Biological activity of DHICA

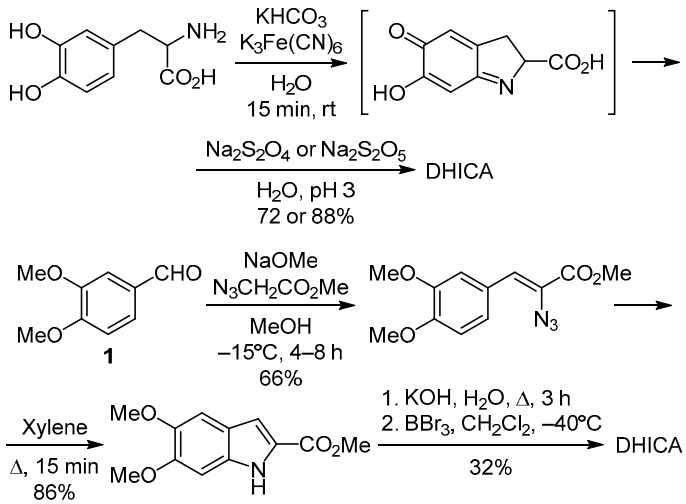
Due to their low molecular weight and small molecular size, endogenous melanin precursors have advantages over final biopolymers as therapeutic agents. First of all, melanin precursors are distinguished by better penetration into tissues and, as a result, have a more pronounced protective function. Studies on the biological properties of melanin precursors and their analogs began relatively recently, and the analgesic effect of DHICA in mice was soon discovered.[5] Like melanin, DHICA has a cytotoxic effect, in particular on the MT-4 line of tumor cells.[6] Esposito et al. confirmed the previously discovered[7] ability of DHICA to inhibit both RNA-dependent DNA polymerase and HIV-1 integrase.[8] In general, the biological effect of DHICA turned out to be similar to that of melanin and is manifested when it is introduced into the body in smaller quantities than the amount of melanins required for the same effect. However, it is not yet clear whether this is due to the intrinsic activity of DHICA or to the fact that upon entering the cell it is further converted into melanin, which has the corresponding effect. Of the known drugs, the closest structural analog of DHICA is the antiviral drug Arbidol which contains a hydroxyindole carboxylic acid fragment, exhibits a wide spectrum of antiviral activity, and is used in complex therapy for the treatment of SARS coronavirus 2.[9]



DHICA synthesis methods

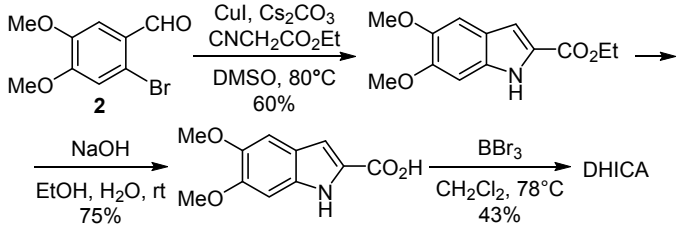
The classical method for the synthesis of DHICA is the oxidation of 3,4-dihydroxyphenylalanine. Hexacyanoferrates and other compounds are used as an oxidizing agent, while the formed intermediate dopachrome is converted into DHICA by the action of $Na_2S_2O_4$[10] or $Na_2S_2O_5$.[11]

Another method for preparing DHICA is a four-step method involving the Hemetsberger–Knittel indole synthesis.[12] In the first step, the condensation of veratric aldehyde (**1**) with methyl azidoacetate is carried out. Subsequent thermal generation of nitrene and its cyclization into an indolecarboxylic acid ester followed by hydrolysis gives DHICA methylated at the phenolic hydroxyls. The protective methyl groups are removed with BBr_3.[13]

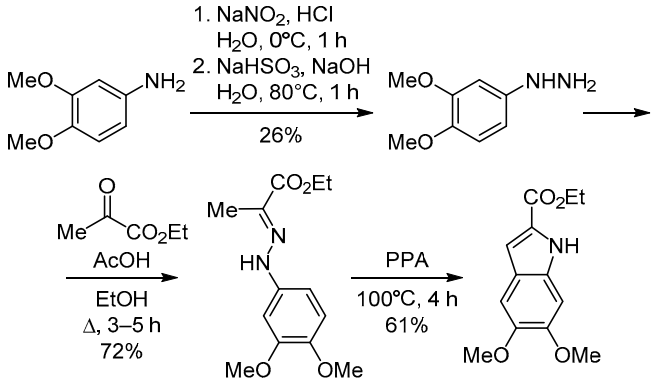


DHICA synthesis methods (continued)

For the synthesis of DHICA, the authors[14] used a route involving the CuI-catalyzed coupling of 2-bromo-4,5-dimethoxybenzaldehyde (**2**) with ethyl isocyanoacetate which was followed by cyclization leading to an ester of 5,6-dimethoxyindole-2-carboxylic acid. Hydrolysis of the ester group and demethylation using BBr_3 afforded the target compound.



To access 5,6-dimethoxyindole-2-carboxylic acid, the key intermediate in the synthesis of DHICA, the classical Fischer indole synthesis is used by rearrangement of [(3,4-dimethoxyphenyl)hydrazono]pyruvic acid ethyl ester into indole-2-carboxylic acid ethyl ester by heating in polyphosphoric acid.[12]



Conclusions

To conclude, the discussed methods for obtaining DHICA are multistep, which makes it urgent to develop new approaches to the synthesis of DHICA in order to increase the availability of chemical precursors for the creation of new medications.

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