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METHODS FOR OBTAINING NEW DERIVATIVES OF THE ALKALOID DONAXIN AND DETERMINATION OF PHYSIOLOGICAL ACTIVITY

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Abstract
Alkaloids - organic alkalis of plant, less often of animal origin. It has long been known that many plants, taken orally in the form of a powder or other form, have a strong effect on the human body - either as strong poisons, or as healing agents. Alkaloids are endowed with more or less pronounced alkaline properties, due to which they easily form with acids salts, and they directly combine with acid elements without the release of water, that is, they relate to acids in the same way as ammonia or its organic derivatives (amines, imines, etc.), and ammonium salts are formed, otherwise ammonia, type (see . Ammonia). The following article looks into the methods of obtaining new derivatives of alkoloid.

Key words: alkoloid, natural compounds, vitamin, amino acids, peptide, marine alkoloid.

INTRODUCTION

Alkaloids are natural compounds (natural products) that contain nitrogen and have significant biological activities. They generally have chemical properties similar to bases. Some nitrogenous compounds derived from plants are not alkaline, but are still classified as alkaloids because of their obvious biological activity. It can be seen from the chemical structure of alkaloids that most of them have a complex nitrogen heterocyclic structure, with only a few organic amine alkaloid compounds not exhibiting such a structure. The definition of alkaloids by the International Union of Pure and Applied Chemistry (IUPAC) is not strict and exact. For example, some vitamins, amino acids, peptides and other nitrogenous compounds derived from natural products do not belong to the category of alkaloids. Alkaloids are widely distributed in nature, especially in plants, and also in animals, microorganisms and marine organisms. There are many known types of alkaloids, with around 10 000 of them having structural formulas that have not yet been fully determined. As there are many types of alkaloids, each of which has a different structural formula, their properties are different from each other. However, the levels of alkaloids contained in living organisms are small, and this is similar in human beings. It has long been recognized that some plants or extracts containing alkaloids can cure diseases or be used as poisons. Since 1806,

when the German pharmacist Serturner isolated morphine from poppies, there have been more than 6000 alkaloids isolated from plants and animals. Through the joint efforts of medical chemists, pharmacologists and other scholars, people have found that a variety of alkaloids have anti-tumor, anti-bacterial, anti-viral and other biological activity. So far, nearly 100 alkaloid compounds have been previously used or are currently being used in clinical trials. In the treatment of many diseases, many alkaloids make good medicines, but some alkaloids can be used to make pesticides for agriculture. Because of their wide range of biological activity, alkaloids are of great interest.

MATERIALS AND METHODS

The ocean is the birthplace of life and is rich in biological materials, making it a huge natural products screening resource. So far, researchers have found more than 300 000 species of marine organisms in the ocean and more than one million new species are thought to be undiscovered. Marine organisms are secondary metabolites, which have formed and accumulated a large number of special chemical structures, significant biological activity in the process of long-term evolution, metabolism in special environments such as high salt, high pressure, low temperature, hypoxia, and lack of light. As such, they show significant anti-viral, anti-inflammatory and anti-tumor properties, among others. Marine alkaloids are a secondary metabolite of marine organisms, mainly derived from marine organisms such as sponges, algae, coelenterates and tunica. Marine alkaloids are alkaline natural products that have important biological activity, the chemical structures of which include amine nitrogen functional groups and a complex carbon skeleton ring. The main biological activities of marine alkaloids are their anti-tumor, anti-viral, anti-malaria, anti-fungal and anti-osteoporosis properties. Many marine alkaloids may be used as anti-tumor, anti-viral and anti-fungal clinical drugs or as the lead compounds for structural modification, as they have good medicinal prospects. In recent years, marine drugs research has been paid more and more attention by scholars, especially in the field of marine alkaloid drugs. Many types of marine alkaloids have been found and extracted from marine organisms, but most often the extraction quantity is small and the efficiency is low.

Alkaloids are produced by a large variety of organisms including bacteria, fungi, plants, and animals. They can be purified from crude extracts of these organisms by acid-base extraction, or solvent extractions followed by silica-gel column chromatography. Alkaloids have a wide range of pharmacological activities including antimalarial (e.g. quinine), antiasthma (e.g. ephedrine), anticancer (e.g. homoharringtonine), cholinomimetic (e.g. galantamine), vasodilatory (e.g. vincamine), antiarrhythmic (e.g. quinidine),

analgesic (e.g. morphine), antibacterial (e.g. chelerythrine), and antihyperglycemic activities (e.g. piperine). [failed verification] Many have found use in traditional or modern medicine, or as starting points for drug discovery. Other alkaloids possess psychotropic (e.g. psilocin) and stimulant activities (e.g. cocaine, caffeine, nicotine, theobromine), and have been used in entheogenic rituals or as recreational drugs. Alkaloids can be toxic too (e.g. atropine, tubocurarine). Although alkaloids act on a diversity of metabolic systems in humans and other animals, they almost uniformly evoke a bitter taste.

The boundary between alkaloids and other nitrogen-containing natural compounds is not clear-cut. Compounds like amino acid peptides, proteins, nucleotides, nucleic acid, amines, and antibiotics are usually not called alkaloids. Natural compounds containing nitrogen in the exocyclic position (mescaline, serotonin, dopamine, etc.) are usually classified as amines rather than as alkaloids. Some authors, however, consider alkaloids a special case of amines.

One of the urgent problems of modern chemical science is the search for the methods of reason able use of n atural plant raw material and preparation of new biologically active compounds on this basis. Among numerous n atural alkaloids that are widespread in the flora of Kazakhstan, a special place is occupied by commercially available alkaloid cytisine extractable from Thermopsis lanceolata; it possesses an aleptic and anti-tobacco activity . It is known that the inclusion of other pharmacophore fragments, including physiologically active heterocyclic compounds, into the structure of plant alkaloids comprises one of the basic approaches in the chemical design of new biologically active substance. Among numerous derivatives of alkaloid cytisine, the compounds with other kinds of biological activity differing from that of alkaloid itself are permanently discovered: hypolipidemic, anti-inflammatory, cholinotropic , hemostatic , antiarrhythmic [One of the interesting ways to modifythioamide fragment; these derivatives possess diverse kinds of biological activity and unbeaten pharmacological value . It is known that thioamides are one of the most important classes of organic compounds and are widely used either in organic synthesis or in industry, agriculture and medicine. The majority of thiourea derivatives possess valuable pharmacological properties and find application as antituberculous, antitumour, anti-inflammatory, antimicrobial, antiulcer and other therapeutically active agents. As a rule, the derivatives of thiocarbamide are obtained by means of the direct substitution of one or two amino groups of thiourea molecule itself by a fragment of primary or secondary amine with the evolution of ammonia. This method has a limited application because it directly depends on the basicity and stability of the initial amine.

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For the purpose of obtaining monosubstituted derivatives of thiocarbamide on the basis of alkaloid cytisine 1, condensation of thiourea with a small excess of cytisine was performed. Condensation of thiourea and cytisine was carried out in the melt at a temperature of 180190 °Ñ for 2030 min until ammonia evolution stopped.

Thus formed cytisino-N-thiocarbamide 2 after several recrystallizations from 90 % ethanol was isolated as a while crystalline substance with high melting point.

A peak of the molecular ion 249 [M+] with relative intensity of 100 % was detected in the mass spectrum of the synthesized cytisino-Nthiocarbamide 2, which can be the evidence of the high stability and thermal stability of compound 2 under the action of electron impact, and rather high strength of the NC(S) bond. BAccording to the data of 1 H NMR spectroscopy, in addition to the protons of the alkaloid fragment, compound 2 contains a broadened singlet of the protons of primary amino group of the thiocarbamide fragment at 4.74 ppm. The introduction of thioamide fragment into the structure of alkaloids broadens the boundaries within which the structures of these n atural compounds can be modified, and can promote new kinds of biological activity. The interaction of the esters of isothiocyanic acids with amines is considered as an ideal method of thiocarbamide synthesis [11].

For instance, in the synthesis of thiocarbamide derivatives on the basis of alkaloid cytisine was carried out from acetal isothiocyanates obtained according to the procedure described in. The synthesis was carried out in alcohol medium through the direct addition of cytisine to propargyloxyethoxyethylisothiocyanat e and 1- phenyloxyethoxyethylisothio-cyanate. An alysis of the mass spectrum of compound 3 revealed the peaks with the following m/z values and relative intensity (Jrel): molecular ion 375 [M]+ (7 %), fragments of decomposition under the action of electron impact on cytisine framework, thiocarbamide and acetale residues =N+ 189 (51 %), NC(S)NH(CH2)2 276

(55 %), =NC(S)+ 233 (40 %), Ñ5Í8NÎS+ 130 (56 %), Ñ5Í8NÎ2S+ 146 (67 %) and propionic fragment ÑÍ2Ñ≡ÑÍ+ 39 (100 %).

In connection with the fact that acetale compounds are rather easily hydrolyzed in the presence of acids, we carried out the soft hydrolysis of compound 3 into cytisino-N-(2-hydroxyethyl)thiocarbamide 4 through boiling of the alcohol solution of compound 3 in the presence of several drops of acetic acid.

CONCLUSION

In this process, cytisino-N-(2-hydroxyethyl)thiocarbamide 4 was isolated with a high yield. The structure of cytisino-N-(2-hydroxyethyl)thiocarbamide 4 formed by hydrolysis was confirmed by means of X-ray structural an alysis, mass spectrometry. Thus, the 1 H NMR spectrum exhibits, in addition to the

protons of the alkaloid fragment, methylene groups and a clear tri plet at 4.53 ppm related to the hydroxyl proton of the primary hydroxy group.

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