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Mini Review

The Synthesis of 4-Nitro-3 (5)-Pyrazolecarboxylic Acids and Study of the Anti-Burn Activity of their Salts with Chitosan

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Abstract

The directed modification of biologically active substances is one of the main approaches to molecular design and is an urgent problem in medicinal chemistry. The presence of free amino groups in the chitosan molecule makes it possible to synthesize various classes of chitosans, which exhibit increased activity compared to the original chitosan. The traditional methods for modifying chitosans based on covalent bonding formation with chemical groups, which is usually difficult to perform compared to quaternization. Since both chitosan and pyrazoles exhibit a broad spectrum of biological activities, the aim of this work is to synthesize 4-nitro-3(5)-pyrazole carboxylic acids and to study their anti-burn activity based on prepared quaternary ammonium salts

Keywords: Synthesis; Modification; Chitosan; Nitropyrazole; Alkylation

Introduction

Over the past decade, the pharmaceutical industry has been actively researching the search for new drugs containing a heterocyclic moiety in their structure. The research in this field has led to the creation of a significant number of effective new generation drugs [1]. There are known many pyrazole compounds in literature [2,3] that have been included in the composition of medicines of unnatural origin. These compounds have been developed and supplied in drug market. Thereby, synthetically available pyrazole derivatives make it possible to predict the commercial value of these compounds as biologically active fragments in pharmaceutical products. Undoubtedly, the expansion of research work in this field has both theoretical and practical interest. The development of chemistry of 3(5)-methylpyrazole is intensively [4] based on its affordable and environmentally expedient production method from the waste-diacetylene with hydrazine [5]. The interest in chitin and chitosan is associated with their unique physiological and ecological properties, such as biocompatibility, biodegradation, physiological activity in the absence of toxicity, anti-burn activity, chelating ability, etc. [6,7]. Chitin or N-acetyl-D-glucosamine is one of the most abundant naturally occurring polysaccharides [8] among biopolymers, and it ranks second after cellulose [9]. The insolubility of chitin limits the scope of its application. From this point of view, the most promising derivative of chitin are its deacetylated derivative chitosan [10]. The physicochemical and biological properties, as well as the published results of their application, make it possible to consider chitosan and its derivatives as a promising raw material for the production of drugs with various pharmacotherapeutic actions.

The Approaches to the Synthesis of 4-Nitro-3 (5) -Pyrazole Carboxylic Acids and their Salts with Chitosan

The high reactivity of 3-methylpyrazoles is associated with their complex structure and the possibility of tautomerism [11]. The phenomenon when a substance can exist in the form of several isomeric forms is called tautomerism [12].The transition forms to each other are called tautomers, and their mutual transition is called tautomeric transformation [13] (scheme 1).Naturally, within the oxidation of 4-nitro-3(5)-methylpyrazole [1], as a result forming the mixtures of two tautomers - 4-nitro-3-pyrazole carboxylic - and 4-nitro-5-pyrazole carboxylic acids [2,3], (scheme 2). This type of tautomerism, caused by the oscillation of a proton

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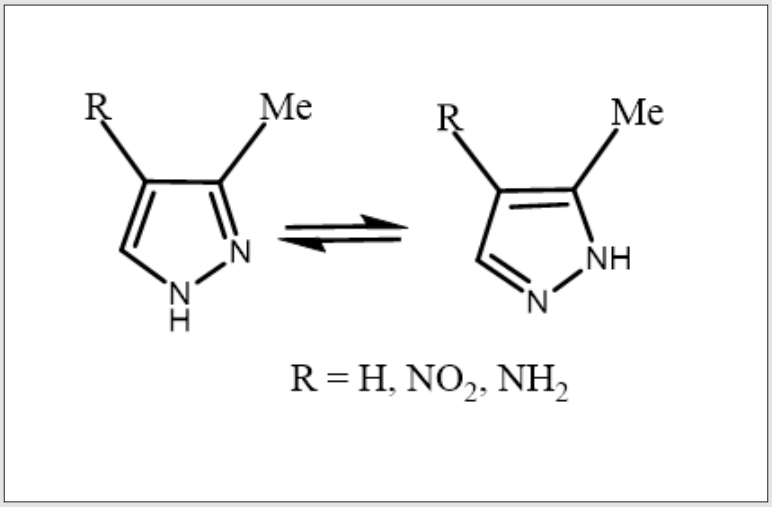
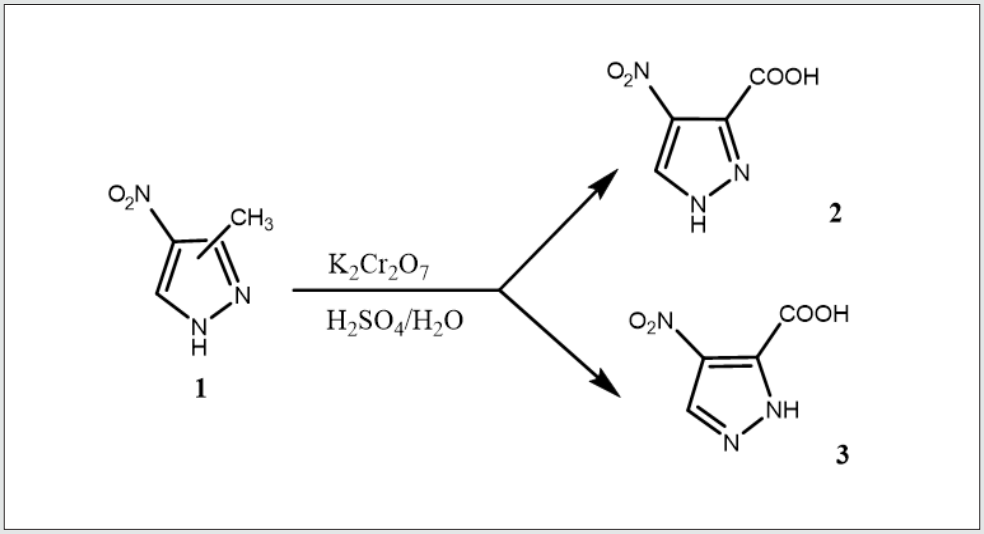
between two nitrogen atoms, Hunter is called, mesohydrogen *tautomerism"* and noted the futility of their isolation [14].The ring of 3(5)-methylpyrazole as an aromatic compound is extremely resistant to various oxidants. Therefore, when interacting with various oxidants in an aqueous medium in the presence of sulfuric acid, only the methyl group is oxidized (Scheme 2) [5].



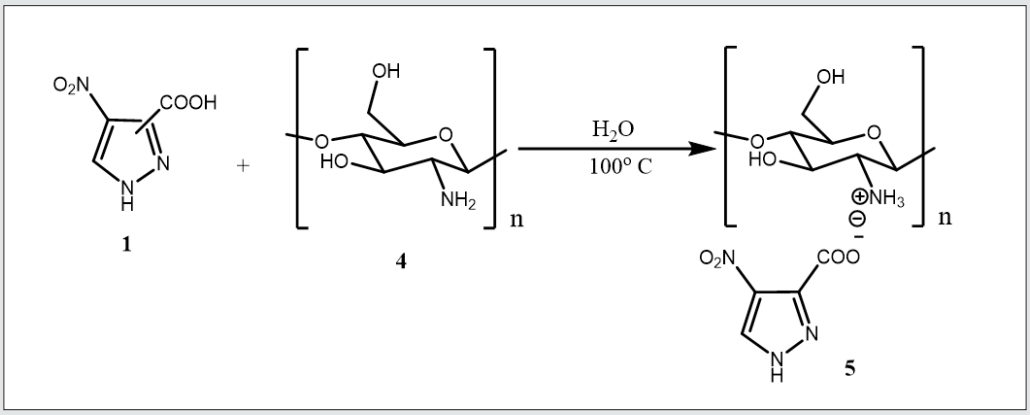
Scheme 1: The approaches to the synthesis of 4-nitro-3 (5) -pyrazole carboxylic acids and their salts with chitosan.



Scheme 2: Mesohydrogen Tautomerism.

The Study of the Anti-Burn Activity of Chitosan Salts

The most important tasks of regenerative medicine is the development of anti-burn coatings, biocompatible with the body and capable of dissolving in the process of wound healing, which do not leave pathological traces and do not cause intoxication of the body with decay products. Taking into account that one of the promising natural polymers used to create such biotransplants that is chitosan as well as its modified derivatives [15], the obtained new modifications and the study of their biological activities seem to be a very urgent task. Therefore, the aim of this work was to develop new drugs based on chitosan [4] and 4-nitro-3 (5) -pyrazolecarboxylic acids [2] for the treatment of thermal lesions of dermal tissues, as well as the establishment of the peculiarities of the effect of the obtained compounds on the course and dynamics of the phase development of a burn wound at different times of the experiment. The corresponding salts of chitosan (5) of 4-nitro-3(5)-pyrazole carboxylic acids (2) were obtained by the general method for the preparation of chitosan salts as a described in [16]. The reaction of pyrazole carboxylic acids [2,3] with chitosan (4) proceeds easily when boiled in water for 5 minutes (scheme 3).



Scheme 3: The study of the anti-burn activity of chitosan salts.

After filtration and removal of insoluble residues, the resulting solution was spray dried to form films. The anti-burn activities of 4-nitro-3 (5) pyrazolecarboxylic acid [2,3] and high-molecular-weight chitosan [4], as well as chitosan salts of 4-nitro-3 (5)-pyrazolecarboxylic acid (5) were studied. On the 15th day after the burn under the action of compound **5**, the dynamics of restoration of the epidermal tissue of white rats is observed. The processes of subtitual regeneration with the restoration of cellular elements and the formation of hair follicles characteristic of healthy skin tissue are noted. The area of destructive foci decreases with the activation of the processes of regeneration of the skin tissue. On the 20th day of the experiment, under the action of compound 5, the regeneration processes are thoroughly completed. Histologically, the formation of the histostructure of the reticular layer of epidermal tissue, where destructive and dystrophic processes reach a minimum, is clearly revealed. Macroscopically, the formation of the hairline in the injured site is clearly distinguished. According to the data of macrophotographic, planimetric and histological studies, it can be concluded that the salt of high molecular weight chitosan of 4-nitro-3 (5) pyrazole carboxylic acid [5] in comparison with the control group and with 4-nitro-3 (5) pyrazole carboxylic acid [2,3]. In addition, chitosan [4] exhibits noticeable anti-burn activity under conditions of experimental thermal burns of the II degree.

Experimental Section

IR spectra were taken on the basis of a spectrometer < Nicolet Avatar 300 FT-YR> on Vaseline oil, ^{1}H and ^{13}C NMR spectra on a << Varian Mercury 300 >> instrument (300 and 75 MHz, respectively, in a solution of DMSO-d6 and D_2O: CF_3COOD). Elemental analysis was performed on a, Eurovector EA 3000'', melting points were determined on a <<Boetius>> apparatus.

4-Nitro-3 (5) -pyrazole carboxylic acid (2, 3)

99.0 g (0.78 mol) of 4-nitto-3 (5)-methyl pyrazole (1) are added into a three-liter flask equipped with a mechanical stirrer, air condenser and thermometer, and 415 ml (7.7 mol) conc. sulfuric acid. The reaction mixture is heated to 60°C and with vigorous stirring, 250 g (0.85 mol) of potassium dichromate is fed in portions over 3-4 hours. After adding the total amount of potassium dichromate, the reaction mixture was heated additional 4 hours, at 60-70°C. Then, the reaction mixture was cooled at 20°C and poured onto an ice: water mixture. The prepared mixture was kept for 2 hours, after which it was filtered to obtain 100-110g of crude product. After recrystallization from the mixture of alcohol: water (200 ml of distilled water and 100 ml of ethyl alcohol are taken per 100 g of the crude product). The recrystallization of 50 g (41%) of 4-nitro-3(5)-pyrazole carboxylic acid [2,3] were obtained, m.p. 225-230°C. IR spectrum, υ, cm^{-1}. 1547.3 (ring), 1692 (C = O), 3235.7 (NH), 3147 (COOH). ^{1}H NMR spectrum (CD_3OD), dpm Hz: 8.45 (1H, s. 5-H), 13.77 (2H, CH_3COOH and NH). ^{13}C NMR spectrum (CD_3OD), d, ppm: 111.8, 132.7 (CH), 140, 160.9 (C = O). Found, %: C 30.28, H 2.30 N 26.38, $C_4H_3N_3O_4$. Calculated, %: C 30.58, H 1.93, N 26.75.

Chitosan salts (5) of 4-nitro-3(5)-pyrazole carboxylic acid (2, 3)

1.57g (0.01 mol) 4-nitro-3(5)-pyrazole carboxylic acid [2,3] and 2.39g (0.0125 mol) chitosan [4] (the degree of deacetylation is DA-75-85%) were boiled at 50 ml of distilled water for 5 minutes by completely dissolution of chitosan, the prepared solution was filtered. In the IR spectra of chitosan 5 salts, absorption of the pyrazole ring at 1529 cm^{-1} and the carbonyl group at 1599 cm^{-1} were observed, as well as stretching vibrations of the CH groups of chitosan at 2853 cm^{-1}, OH and amino group at 3000-3500 cm^{-1}. In contrast to chitosan salt [5], in the IR spectrum of the initial pyrazole, the intensity of the pyrazole ring was observed at 1547.3 cm^{-1} and the carbonyl group at 1692.5 cm^{-1}. It is interesting to note that stretching vibrations of the primary amino groups (3400 cm^{-1}) were almost absent, which indicates the formation of a chitosan salt with 4-nitro-3(5)-pyrazole carboxylic acid [2,3].The ^{1}H NMR spectrum (D_2O-CF_3COOD) in chitosan salts retains the pyrazole ring proton at 8.5 ppm. Comparatively weaker field 3.75-4.25 ppm vibrations of protons of CH and CH_2 groups of chitosan were observed in the form of multiples. Polymer films were obtained from solutions of the advising salt [5] by pouring into polyethylene cups 10 cm in diameter and drying at room temperature.

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