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Synthesis and Biological Activity of Cyanoethyl Derivatives of Fusidic Acid

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Abstract—3,11-Dihydroxy and 3,11-dioxo triterpenoids of the fusidane series reacted with acrylonitrile in 1,4-dioxane in the presence of alkali and phase-transfer catalyst to give mono- and bis(2-cyanoethoxy) and 2-cyanoethyl derivatives. The reaction with 3,11-dioxo analog afforded 2,2-disubstituted derivative as a result of addition of two cyanoethyl groups to the α-position with respect to the C^3=O carbonyl group. The isolated compounds were screened for antibacterial and antifungal activities.

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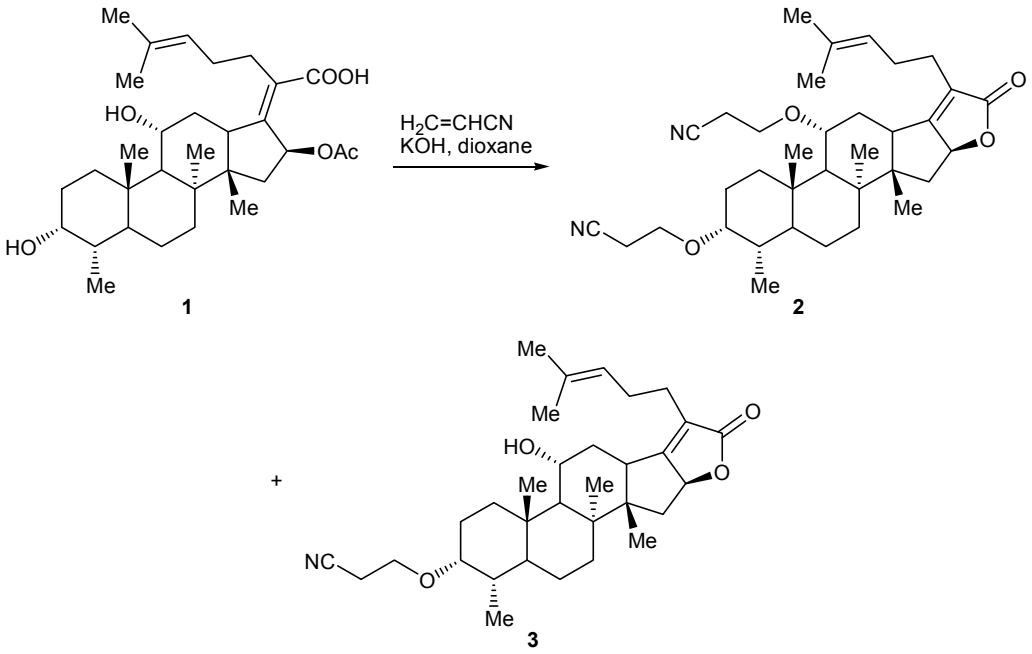
A challenging problem in modern medical practice is therapy of diseases caused by antibiotic-resistant microorganisms [1–3]. The data published by the US Centers for Disease Control and Prevention indicated more than 2 million diseases caused annually by bacteria and fungi that are resistant to at least several classes of antibiotics [4]. Development of new antimicrobial agents remains one of the most important problems of chemistry and medicine. According to the statistical data [5], about ~47% of all practically used drugs created over the past 30 years have been designed on the basis of natural molecules (natural compounds, their semisynthetic analogs, and biomimetics). More than half of antitumor and antimicrobial drugs are of natural origin, or they have been designed by analogy with natural compounds. A huge diversity of natural compounds, the major part of which is represented by plant metabolites, provides an abundant source for rational design of medicines. In this respect, a great role in the design of new therapeutic agents is played by the development of efficient methods of transformations of natural molecules with a view to obtaining their analogs exhibiting a higher activity and selectivity for biological targets and possessing the lowest general toxicity.

Fusidic acid is one of promising natural antibiotics used in clinical practice. It is a tetracyclic 29-nortriterpenoid produced by *Fusidium coccineum* [6] and is successfully used for the treatment of purulent inflammatory diseases of different localizations, caused by (among others) methicillin-resistant *Staphylococcus spp.* [7, 8].

Good results can be achieved by the introduction of a nitrile functionality into natural molecules; the high biocompatibility of cyano group is indicated by wide occurrence of nitriles among pharmaceuticals, as well as by the results of ongoing clinical studies of potential drugs [9, 10]. The cyano group is fairly stable and in most cases is not metabolized in the human organism [11, 12]. Due to diversity of the mechanisms of interaction between the cyano group and biological targets, nitriles attract increasing attention as promising substrates for the design of various medicinal agents [13].

A simple and convenient method for the introduction of a cyano group into organic molecules possessing a labile hydrogen atom is based on cyanoethylation with acrylonitrile. With the goal of extending the set of available antibacterial agents, in the present work we studied cyanoethylation of fusidic

Scheme 1.



acid and its derivatives, and the isolated compounds were tested for antimicrobial and antifungal activities.

The reaction of fusidic acid (**1**) with excess acrylonitrile afforded two products and was accompanied by cyclization involving the 16-acetoxy group and carboxylic acid functionality to form lactone ring. The product mixture was separated by column chromatography to isolate 3,11-bis- and 3-monocyanoethoxy derivatives **2** and **3** in 50 and 40% yield, respectively (Scheme 1). The formation of lactone ring in molecules **2** and **3** was confirmed by the upfield shift of the 16-H signal (δ 4.96 ppm, d.d) in the ^{1}H NMR spectra relative to the corresponding signal of **1**, as well as by the disappearance of signal at δ 1.98 ppm due to acetoxy group. In addition, downfield shift of the C^{16} and C^{21} signals in the ^{13}C NMR spectra was observed.

The presence of cyano groups in molecules **2** and **3** followed from the HMBC spectra which displayed cross-peaks between diastereotopic protons in the β-position with respect to the cyano group and C^3 and/or C^{11}. Furthermore, upfield shifts of the 3-H and 11-H signals (δ 3.28 and 3.84 ppm, respectively) were observed in the ^{1}H NMR spectrum of **2**. In the ^{13}C NMR spectrum of **2**, carbon nuclei of the cyano groups resonated at δ_C 118.41 and 118.70 ppm, and the CN signal of **3** was observed at δ_C 118.56 ppm. The C^3 and C^{11} signals in the ^{13}C NMR spectrum of **2** shifted downfield to δ_C 79.91 and 75.90 ppm, respectively.

Taking into account that cyanoethylation of **1** under the given conditions was accompanied by lactonization, we presumed that cyanoethylation of a compound already containing lactone ring would improve the selectivity. By alkaline hydrolysis of fusidic acid (**1**) we obtained lactone **4** in 95% yield. In fact, the cyanoethylation of **4** was characterized by complete conversion and high chemoselectivity. After purification

Scheme 2.