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BASIC PRINCIPLES OF SYNTHESIS AND CONFORMATIONAL ANALYSIS OF ACETYLENE AND BIOLOGICALLY ACTIVE COMPOUNDS

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Annotation:
The article focuses on the synthesis of enyne triols and their stereochemical and conformational features. The preparation of Z- and E-isomers, their separation, and structural confirmation through spectroscopic methods are described. Analysis of NMR spectra and anisotropy calculations revealed conformational differences between the isomers. Pharmacological studies demonstrated that the synthesized enyne triols exhibit significant choleretic activity, with E-isomers being more active than Z-isomers. These findings highlight the potential of enyne triols as promising candidates for the development of new therapeutic agents.

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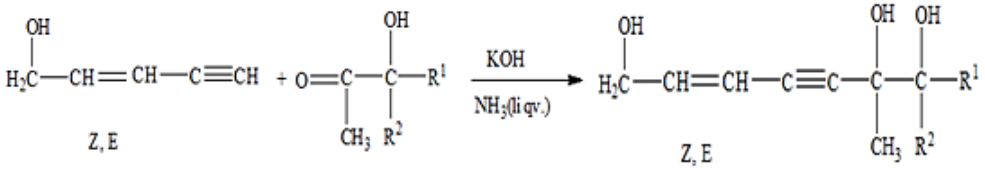
Currently, organic chemistry is undergoing a period characterized by in-depth studies of the structural properties of molecules, the nature of intramolecular interactions and stereochemistry, and the determination of the essence of "structure-activity" relationships on the basis of these studies.

The relevance of this work is associated with the formulation and resolution of a number of fundamental questions regarding the synthesis, stereochemistry and pharmacological activity of compounds containing heteroatoms, acetylene and ethylene fragments. These compounds serve as

model compounds for resolving key questions regarding the configurational and conformational stability of molecules.

The purpose of this study is to develop methods for the synthesis of previously unknown enyne triols, to study the chemical properties, stereochemistry and conformational properties of the synthesized compounds, and to elucidate their pharmacological activity in order to create new therapeutic agents.

By condensing a mixture of Z, E-isomers of enyne alcohol with hydroxyketones, we obtained geometric isomers of primary-di-tertiary enyne triols. The reaction was carried out in liquid ammonia at -35° C in the presence of powdered potassium hydroxide, the amount of which was calculated as 2 moles per mole of the starting enyne alcohol. Under these conditions, the condensation proceeds to form a mixture of Z- and E-isomers of enyne triols in 67-75% yield, respectively. The ratio of Z- and E-isomers was determined from the integrated intensity of the 1H NMR spectra, and the configuration assignment was carried out according to the coupling constant.



(1 Z,E)R^1= R^2= CH_3; (2 Z,E)R^1= C_2H_5,R^2= CH_3;

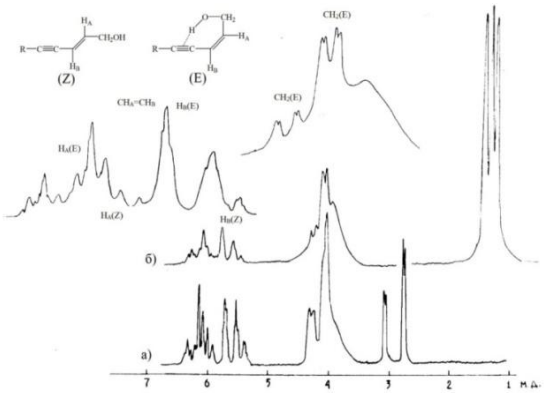
(3 Z,E)R^1= C_3H_7,R^2= CH_3; (4 Z,E)R^1= C_4H_9,R^2= CH_3;

(5Z,E)$R^1 + R^2$= $(CH_2)_5$;

Separation into separate Z and E isomers was carried out using silica gel column chromatography. The composition of the geometric isomers of the synthesized primary-ditertiary enyne triols (1 Z, E – 5 Z, E) was confirmed by elemental analysis, and their structure was confirmed by IR and PMR spectra, as well as by reverse Favorsky decomposition with starting reagents in the presence of a small amount of potassium.

The results of pharmacological tests showed that the enyne triols obtained by us have a higher choleretic activity than dihydrocholic acid, a medicinal product used in clinical practice.

In the PMR spectra of the compounds (1 Z, E – 5 Z, E) (Fig. 1), the signals from the methylene protons of the Z and E isomers appear as two doublets of doublets. The difference in the chemical shift of the OCH2 group signals in all cases exceeds 0.2 ppm, which is due to their different orientations relative to the magnetic anisotropic acetylene bond. To determine the reasons for the differences in the PMR spectra of the OCH2 groups, their anisotropic chemical shifts were calculated using the McConnell equation. The geometric parameters required for the calculation included in this equation were obtained from a schematic representation of the most probable conformations based on known angles and interatomic distances. When choosing these conformations, the possibility of intramolecular hydrogen bonding in the Z-isomer was taken into account.



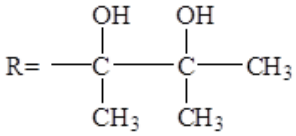


Figure 1. NMR spectra of: a) the initial single alcohol (R = H) b) a mixture of Z, E-enyne triols (1Z, E)

Information on the preferred conformation of enyne triols was obtained by comparing the calculated anisotropic chemical shifts of the methylene protons of the geometric isomers. Figure 2 shows four conformations in which the methylene protons are located relative to the magnetically anisotropic acetylenic and ethylene bonds.

For the Z-isomer, based on the NMR spectra of the initial enyne alcohol, it can be assumed that there is mainly one conformation (II), shown in Figure 2. For the E-isomer, if the condition of geminal equivalence of the methylene protons is met, two conformations (III) and (IV) are possible, in some cases located at a distance and in close proximity to the ethylene bond. In the conformation (IV) state (Fig. 2), there are two destabilizing factors: the electrostatic interaction of the unshared electron pair of oxygen and the p-electrons of the acetylene bond, as well as the spatial proximity of the HB proton and the OH group, so the conformation looks more favorable (III).

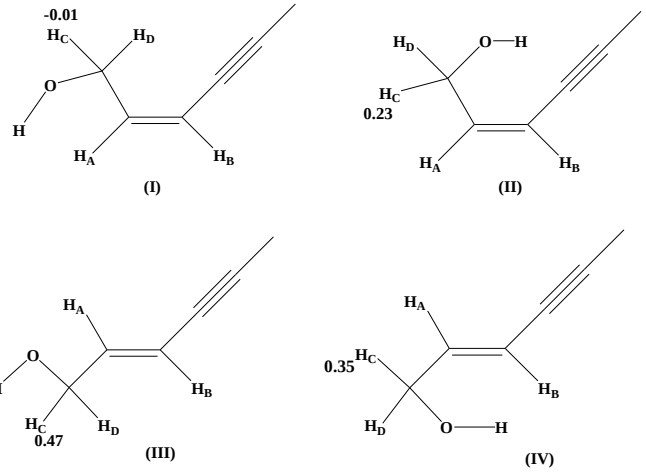
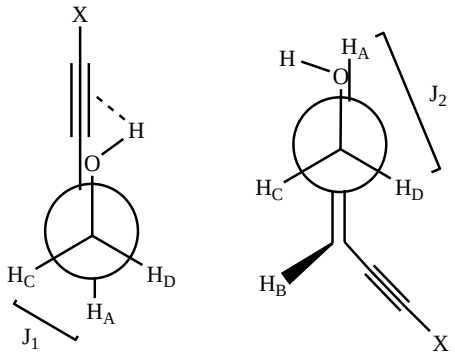


Figure 2. Possible conformations of enyne triols (1 Z, E -5 Z, E)

As can be seen from the Newman projections shown in Figure 3, the dihedral angles between the HA protons and the HC and ND protons in conformation (II) are approximately 60°, while in conformation (B), corresponding to conformation (III), they are 120°. Based on the angular dependence of the Karplus coupling constant, one would expect a larger coupling constant between the HA proton and the methylene group in the (Z) isomer, $J_{CH_2'H_A'} < J_{CH_2H_A}$, as observed by inspection.



(II) (III)

Figure 3. Newman projections obtained by rotating the carbon atoms of the methylene group and the bond connecting the ethylene bond.

Thus, based on the analysis of the nature of the magnetic anisotropy of the acetylenic bond in neighboring protons and the analysis of the coupling constants, it was found that the conformational difference between the Z- and E-isomers is due to the intramolecular interaction of the OH group (p-electrons of Z-Figr3).

Pharmacological studies of enyne triols revealed the presence of choleretic activity in this class of compounds. It was shown that the E-isomers are more active than the Z-isomers, which is associated with the conformational properties of the Z, E-isomers of enyne triols.