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Stachybotrys Chartarum Secondary Metabolots of Poisonic Microzoquary

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ABSTRACT

Filtered culture fluids of the *Stachybotrys chartarum* strain were exhaustively extracted with ethyl acetate. The iso lated red residue was subjected to column chro matography (silica gel) with gradient elution, resulting in 2 different fractions. Fraction 1-2 consisted of a crystalline material that showed the same parameters of ^{1}H and ^{13}C as the parameters of staxibotrilaktam and staxibotrilaktam A, a derivative of driman's sesquiterpenoid. The structure proposed for this compound was based on spectroscopic data and no indication of the configuration of stereogenic carbon atoms was obtained. The fungus was produced mainly stachybotrys fully characterized derived sesquiterpenoid of drimana.

KEYWORDS: Tachybotriotoxicosis, extraction, column, spectrum, silufol, chromatography, strain, microgribs.

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Many poisonous fungi cause mycoses and harm human and animal health. It is known that fungi are sometimes causative agents of chronic hemorrhoids, dermatophytosis, hair loss and eye diseases [1-5].

Food poisoning and nutrition with toxins (poisons) of fungi cause mycotoxicosis in humans and animals. The “moldy bread” phenomenon occurs when the grain is contaminated with Fusarium fungi. The poisonous properties of mushrooms are retained even when bread is baked from them [6,7].

In such a situation, it became necessary to get acquainted with the results of the study of toxin-producing fungi, to determine their origin, distribution in nature and, on this basis, to create a system for combating the diseases they cause. In this regard, the study of toxin-producing fungi is one of the urgent problems of science and requires extensive research by specialists in various fields at the modern level of scientific practice [8].

Extraction. The nutrient medium plays an important role in the growth, development and synthesis of secondary metabolites of microorganisms; the growth of microbial cells at temperatures optimal for their development ensures the maximum formation of secondary metabolites in the environment. In studies, the effect of nitrogen sources on the synthesis of secondary metabolites of the *Stachybotrys chartarum* strain was studied and the salts NH_4NO_3, $(NH_4)_2SO_4$, $(NH_4)H_2PO_4$ and $NaNO_3$ were used in the experiments. The experiments were carried out at 35 and 45°C, depending on the optimal temperature for the development of the strains selected for the study. *The Stachybotrys chartarum* strain was grown on Mandels' nutrient medium for 14 days using a shaker in a 20 L flask. When the micelles of the cultured Stachybotrys chartarum strain were filtered from the culture broth, 58 g of micellar biomass and 15 L of the culture broth were obtained. Filtered 58 g of micellar biomass was placed in a flask with 200 ml ether and heated in a water bath at 40–450 ° C. The extraction process was repeated three times, and 6.95 g of extraction was obtained. The remaining aqueous portion was extracted with chloroform, and when the extract was dried using a vacuum rotary equipment, an extraction total of 1.32 g was formed. The total extraction weight was 8.27 g. *Stachybotrys chartarum* adsorbed 8.27 g of the extracted amount on 250 g of Silpearl silica gel. The adsorbent was placed on a column chromatographic column. The column was sequentially washed with an elliptical system benzene: methanol (10: 1) and benzene: methanol (1: 1). Using column chromatography, 83 mg of stachibotrilactam A (I) was obtained by washing with benzene: methanol (10: 1) and 95 mg of stachibotrilactam

was obtained by washing with benzene: methanol (1: 1) and elution.

Staxibotrilactam.$C_{23}H_{31}NO_4$, суюқ.тем.200°C (MeOH), Rf=0,45.(ЮҚХ, sulifol, system C_6H_6-MeOH, 1:1), $[\alpha]_D^{24}$-12,5 ± 2°(c 0,8; $CHCl_3$-MeOH, 1:1).

IQ-spektr (KBr, ν, $см^{-1}$): 3350-3140; 1675; 1650; 1630; 1475; 1360.

Mass -spektr, m/z (%): M^+385 (95)[429,2483; $C_{25}H_{35}N0_5$], 411 (17,5) [411, 2401; $C_{25}H_{33}NO_4$], 398 (100), 396 (11,3), 386 (16,3) [386, 2319; $C_{23}H_{32}NO_4$], 380 (10) [380, 2251; $C_{24}H_{30}NO_3$], 368 (2,8), 354 (2), 342 (1,9), 339 (1,8), 312(1,9), 300 (3), 287 (3,3), 274 (10), [274, 1097; $C_{15}H_{16}N0_4$], 260 (10), 256 (7,5), 242 (10), 234 (12,5), 223 (30), 221 (20), 207 (12,5), 189 (15),[189,1649;$C_{14}H_{21}$], 149 (12,5), 135(12,5),129(12,5),109(12,5).

PMP spektrs (100 МГц, CD_3OD, δм.у., J, *Гц*):0,70 (CH_3- 18, д, ^3J=7 Гц), 0,85; 0,93; 1,01(3xCH_3, с), 2,79; 3,20 (2H-11, д, ^2J=18Гц), 3,70 (4H-24/25, мsystemsAA'BB'), 4,35 ва 4,55 (2H-22, д, ^2J=18 Гц), 6,65 (H-14, с).

Staxibotrilactam A (I),$C_{24}H_{33}NO_4$, суюқ.тем. 220° (MeOH), Rf=0,52 .(ЮҚХ, силуфол, система C_6H_6-MeOH, 10:1), $[\alpha]_D^{24}$-13,5 ± 2°(c 0,8; $CHCl_3$-MeOH, 10:1).

3-Monoacetatestaxibotrilactam A (II). 9.8 mg of staxibotrilactam A was infused with 0.5 ml of dry pyridine and 0.30 ml of acetic anhydride. The reaction mixture was mixed well and stored in a dark place at room temperature for 1 day. The solvent of the reaction mixture was evaporated and the residual column was chromatographed. Chromatographic column chloroform: methanol (20: 1) was washed with systemic eluent to obtain 7.71 mg of amorphous monoacetate staxybotrylactam A (II), $C_{26}H_{35}NO_5$, Rf = 0.36 (YuQX, silufol, system chloroform: methanol (10: 1).

Chemical structure and modification of staxibotrilactam A. Stachybotrylactam A, one of the important products of the laboratory fungus Stachybotrys chartarum grown under laboratory conditions, was isolated using column chromatography and modified to study its structure (Figure 1).

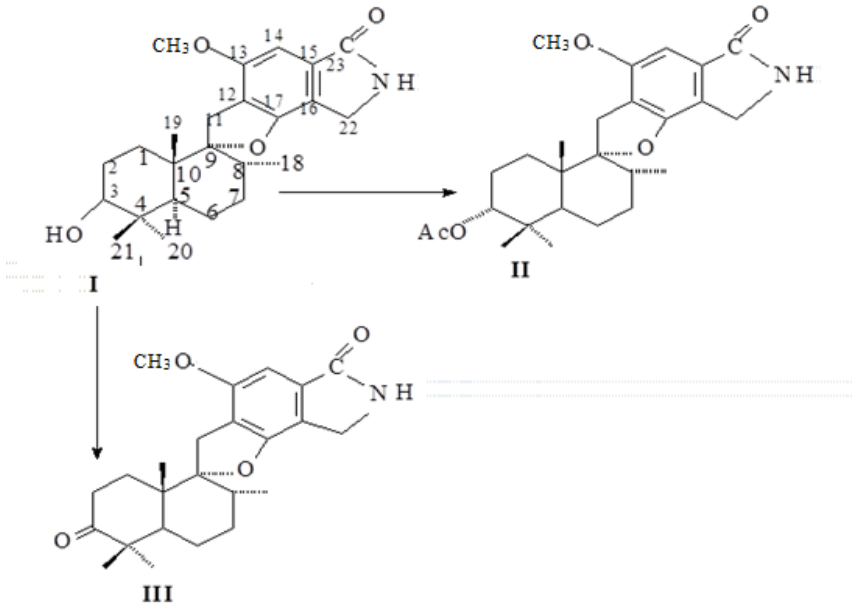

Figure 1. Chemical modification of Staxibotrilactam A

The elemental composition of Staxibotrilactam A was determined with a high-precision mass spectrometer$C_{24}H_{33}NO_4$. NMR 13S spectrum of the substance under investigation (I) (Table 1), 156.88; 155.39; 135.66; 117.60; 113.22; 101.80 m.u. the presence of signals indicates the presence of a five-sided interchangeable benzene nucleus in the stachibotrilactam A molecule. Accordingly, staxibotrilactam A (I) was found to be 7.31 m.u. in the 1M spectrum of NMR (Table 1). The presence of a singlet signal specific to a single aromatic proton indicates the presence of a single aromatic proton.

Table 1. Chemical displacement of stachibotrilactam A (I) and its derivatives (d, m.u.), multiplicity and spin-spin interaction constant (SSTK, J, Gts)

The state of protons	Substances		
	I	**II**	**III**
1α-H	2,35 тд(13;3)	1,56тд(13;3)	1,58тд(13;3)
1β-H	1,13 дт(13;3)	1, 31 дт(13;3)	1, 33дт(13;3)
2α-H	1,70	1,80	1,82
2 β-H	1,95 тт (13;3)	1,55 тт (13;3)	1,55 тт (13;3)
3 β-H	3,54	4,61 т (3)	4,63 т (3)
5 α-H	0,94	0,94	0,96
6 α-H	1,55	1,63	1,65
6 β-H	1,42 кд (13;3,5)	1,38 кд (13;3,5)	1,40 кд (13;3,5)
7 α-H	1,70	1,70	1,72
7 β-H	1,55	1,38	1,40
8 β-H	1,75	1,94	1,96
11 α-H	3,00 д (16,7)	2,98 д, (17)	3,16 д, (17)
11 β-H	3,09 д (16,7)	2,73 д (17)	2,82 д (17)
14-H	7,35 с	7,54 с	7,44 с
18-CH_3	0,80 д (5,8)	0,73 д (6,5)	0,73 д (6,5)
19- CH_3	0,97 с	0,90 с	1,12 с
20- CH_3	1,19 с	0,98 с	1,16 с
21- CH_3	0,88 с	0,89 с	1,06 с
22- CH_3	4,09; 4,35 d (16,7)	4,32; 4,44 d (17)	4,35; 4,40 d (17)
3-OAc	-	2,02 с	-
-OCH_3	3,79 с	3,80 с	3,76 с
NH	7,05	7,08	7,04

The spectrum of staxibotrilactam A **(I)** was recorded in deuteropyridine and the spectrum of substances **II-III** in deuterochloroform solvents. Chemical shear, multiplicity, and spin-spin (SSTK) interaction constants were determined in the correlation spectra 2M NMR 1N-1N, 1N-13S. Abbreviations: s-singlet, d-doublet, t-triplet, dd-doublet-doublet, td-triplet-doublet, dt-doublet-triplet, tt-triplet-triplet, kd-quartet-doublet, m-multiplet.

Interpretation of the interpretive spectra of Stahibotrilactam A NMR 1N, 13S, 2M, NMR 1N-1N and the chemical correlation spectra of NMR 1N-13S is shown in Figure 1, which allows the formation of a fragmented structure. The alicyclic part of the molecule consists of 15 carbon atoms and corresponds to a sesquiterpenoid driman ring structure. When staxibotrilactam A is acetylated with acetic anhydride under pyridine conditions, monoacetate **II** is formed. The formation of monoacetate means that there is a single hydroxyl group in the molecule of staxybotrilactam A **(I)**.The formation of resonance frequencies at 3.79. of the methoxyl group in the NMR 1N spectrum of monoacetate **II** indicates the presence of a methoxyl group belonging to this field and the methoxyl group located in this benzene ring. Indeed, the presence of a signal at 55.56 . belonging to a carbon atom attached to a methoxyl group in the benzene ring in the NMR 13S spectrum proves once again that staxibotrilactam A **(I)** has a methoxyl group in the benzene ring.

A comparative analysis of the PMR spectra of substances **I** and **II** shows that the appearance of a single-proton triplet signal in the PMR spectrum of monoacetate **II** at 2.02 . Therefore, the fact that the corresponding hydroxyl group is located on the secondary carbon and the presence of a signal at 80.06 in the YaMR 13S spectrum of stachybotrilactam A confirms that this signal contains a secondary carbon atom.

The formation of maximal peaks corresponding to m / z 206 formed during the mass spectrometric decomposition of the oxidized III ketone state of stachybotrilactam A indicates that the secondary hydroxyl group in the I molecule

of stachibotrilactam A and the secondary hydroxyl group located in C-3 are oxidized.

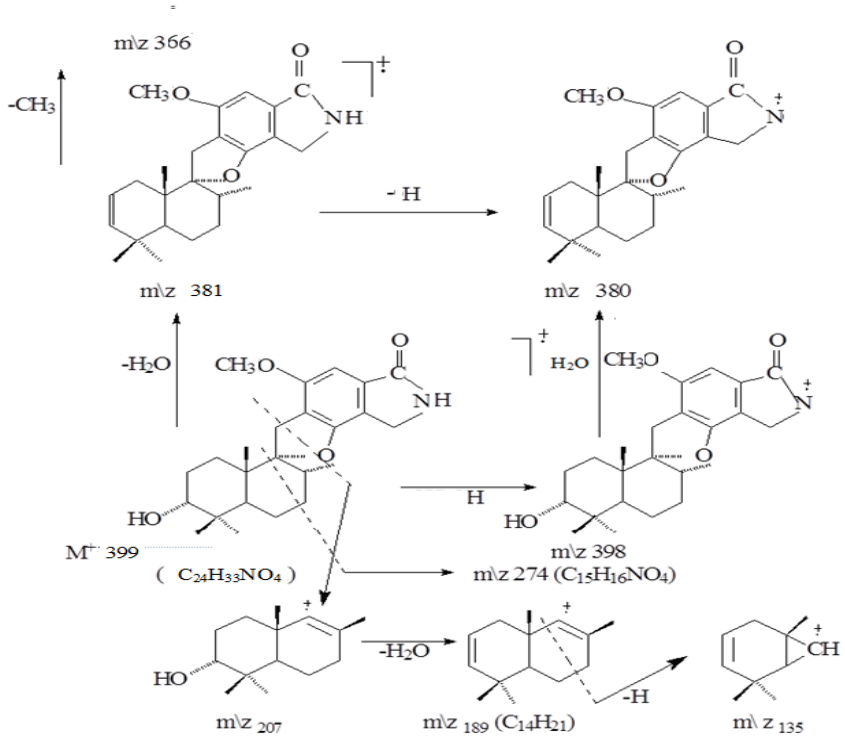

Figure 2. Mass spectrum of Staxibotrilactam A obtained by electron flow

The formation of a signal in the YMR 13S spectrum of stachibotrilactam A (I) in the 173.9 region indicates the presence of a functional group in which the carbamide or isomerization group azometinoxy is regrouped. The choice between them will be made later.

The presence of high-frequency valence oscillations in the 1675 cm-1 region in the IR spectral data of the substance indicates the presence of a complex ether group in the molecule of stachybotrilactam A. From the above data, it can be seen that in the molecule of stachybotrilactam A **(I),** 2 of the 4 oxygen atoms are primary and 2 are secondary, one of which consists of oxygen atoms in the phenolic hydroxide group, one of which is 173.9 m.u. the display of a signal in the field indicates that the oxygen atom is bonded to the quaternary carbon atom. The display of signals at 155.6 and 139.2 m.u. in the NMR 13S spectrum of carbon atoms bound to the aromatic ring indicates that there is another carbon term bound to the oxygen molecule in addition to phenol hydroxyl in the stachybotrylactam A molecule. The presence of a signal at 80.06 m.u. in the NMR 13S spectrum indicates the presence of a repulsive carbon atom attached to the oxygen atom. The appearance of signals specific to carbon atoms at 139.2 and 80.06 m.u. indicates that the aromatic carbon atoms with the alicyclic carbon atom are bonded to oxygen through an epoxy functional bond.

The formation of m \ z 207 and 189 ions during the decomposition of Staxibotrilactam A under the influence of an electron current indicates that the secondary hydroxyl group is located in the sesquiterpenoid part of the molecule, including the primary methoxyl group in the side chain where the C-13 carbon atom is located in the benzene ring.

128.3 of the carbon atoms in the triple-exchanged benzene nucleus; 128.8 and 137.3 m.u. the formation of chemical shifts in the signals in the field allows us to conclude that the aromatic ring is bound by a three-dimensional carbon-carbon bond.

The resonance of two protons of the AV system at 3.00 and 3.09 m.u. in the 1M spectrum of Stahibotrilactam A (I) and their 2M NMR in the ^{1}N - ^{13}C spectrum at 32.86 m.u. resonance of protons with chemical displacement correlation of a carbon (C - 11) atom. In the long-range 1N - 13C (NMVS) correlation spectrum of these isolated methylene protons (Table 4 and Figure 2), three aromatic carbon atoms are C-12 (128.8 m.u), C-13 (139.2 m.u). , With C - 17 (155.6 m.u) and the three carbon atoms in the terpenoid part of the molecule, C - 8 (37.1 m.u), C - 9 (104.7 m.u), C-10 (42, 2 m.u) correlation indicates that these carbon atoms are cross-linked. Therefore, a C-11 carbon atom containing isolated methylene protons binds the sesquiterpene portion of the molecule to a carbon-carbon bond with a C-12 (128.8 m.u.) carbon atom in an resonant ring. The epoxy functional group that binds carbon atoms C-9 (104.7 m.u) and C-17 (155.6 m.u) in the molecule forms a spirobenzofuran ring. In the same NMVS spectrum, the interaction of the aromatic proton N-14 (7.35 m.u.) with the carbon atoms C - 12 (128.8 m.u.), C - 13 (139.2 m.u.) C - 14 (139.2 m.u.) indicates the role of

the proton under discussion in carbon. Similar conclusions can be drawn from a comparison of the PMR spectra of stachybotrilactam A (I) (CD3OD) and monoacetate stachibotrilactam A (II) (CD3OD). The aromatic proton signals in the PMR spectrum of monoacetate stachibotrilactam A (II) (CD3OD) were 0.19 m.u. compared to those of stachybotrylactam A (I) (CD3OD). the presence of a low area indicates that the acetoxyl group in the aromatic proton and metabolite II is viscous. Vicinal correlation of C-23 (173.9 m.u.) and C-16 (137.3 m.u.) carbon atoms with the N-14 hydrogen atom in the aromatic ring is observed. This indicates that the S-15 carbon atom is in the geminal state relative to the aromatic proton. Therefore, the chemical shifts specific to the two protons of the AV system in the NMR ^{1}H spectrum of substance II are 4.09 m.u. and the appearance of a doublet signal at 4.35 m.u. and the correlation of the carbon atom in the 2M YaMR 1N-13S correlation spectrum with the characteristic signal at 43.6 m.u. indicate that methylene protons are located in the S-22 carbon. From the NMVC spectrum of these compounds, C-23 (173.9 m.u.), S-16 (137.3 m.u.), S-17 (155.6 m) of the AV system methylene protons located in the S-22 carbon were considered. u.) and S-15 (128.3m.u.) interact with carbon atoms, indicating that the C-22 carbon atom is bonded to the C-16 atom.

Table 2. Long-range 1H - 13C correlation interaction (NMVC) spectra of dextiropyridine of Staxibotrilactam A (I)

Protons		**Carbon atoms**	
Its place in the molecule	**δ, м.у.**	**Its place in the molecule**	**δ, м.у.**
H-5	0,94	C-4 C-10 C-19 C-21	38,0 42,2 17,4 23,5
2H-11	3,00; 3,09	C-8 C-9 C-10 C-12 C-13 C-17	37,1 104,7 42,2 128,8 139,2 155,6
H-14	7,35	C-12 C-13 C-16 C-23	128,8 139,2 137,3 173,9
CH_3-18	0,80	C-7 C-8 C-9	30,8 37,1 104,7
CH_3-19	0,97	C-1 C-5 C-9 C-10	24,9 41,0 104,7 42,2
CH_3-20	1,19	C-3 C-4 C-5 C-21	80,6 38,0 41,0 23,5
CH_3-21	0,88	C-3 C-4 C-5 C-21	80,06 38,0 41,0 23,5
2H-22	4,09; 4,35	C-15 C-16 C-17 C-23	128,3 137,3 155,6 173,9

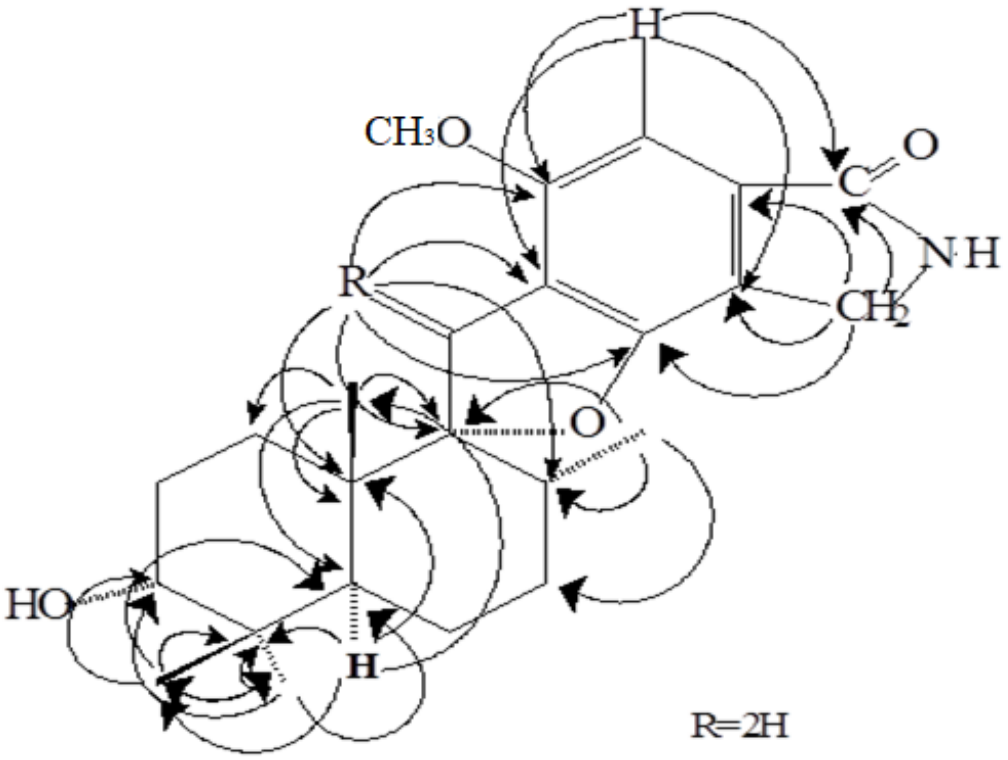

Figure 3. NMVC spectrum of dextropyridine of Staxibotrilactam A (I)

Given the identified parts of the molecule, it follows from the elemental composition of the metabolite **I** being studied, $S_{24}N_{33}NO_4$, that there must be one more cycle in the stachibotrilactam A molecule.

As shown above, we can see from the NMR 13S spectrum that the signals containing the C-23 (173.9 m.u.) carbon atom correspond to the N-bonded urea group or its isomer azometinoxy group.

Demonstration of chemical shifts of hydrogen atoms C-22 (43.6 m.u.) and 2H-22 (4.09; 4.35 m.u.) in the NMR 13S and ^{1}H spectra of Staxibotrilactam A with heteroatoms, especially with the nitrogen atom indicates that it is connected. Thus, the C-23 carbon atom combines with the C-22 atom through the tertiary N atom to form the E heterocyclic ring. The correlation of the signals of N-H hydrogen atoms in the NMVC spectrum of monoacetate **II** with the signals of carbon atoms C-22 and C-23 confirms this conclusion once again.

The addition of A / B rings and the conformation of the terpenoid part of the new **I** molecule are determined as follows. The H-5 proton signal in the NMR ^{1}H spectrum of Staxibotrilactam A is 0.94 m.u. signals are observed in the field of interaction values of spin-spins at (Table 3). These constants indicate that the N-5 proton is axially oriented relative to the V ring in the terpenoid part of the molecule, which indicates that the A and B rings are trans-positioned relative to each other. However, the spatial arrangement of H-1α, H-1β, H-2β, H-3β, H-6βprotons in the PMR spectrum of **I-II** compounds (Table 3) shows that it has a structure (Figure 4).

In the PMR spectrum (SDCI3) of acibotrilactam A acetates **I** and **II,** the H-3 proton signal is 4.61 and 3.54 m.u. the appearance of triplet signals in the field is observed when the interaction constant of the spin-spins has a constant power at values in the field 3J = 3Gts.(^{3}J = 3Гц) From the data given, it can be seen that the chemical displacement parameters of the H-3 proton indicate that the free hydroxyl group C-3 containing monoacetate **II** is in carbon and therefore the resulting product II is monoacetate of stachybotrilactam A. Ketone III obtained by oxidation of monoacetate II according to the Jonsu method is 3 - dehydrostaxibotrilactam A. The formation of a triplet signal in the range of values of the spin-spin interaction constant (^{3}J = 3Gts) indicates the spatial location of the H-3 proton in the β -equatorial direction. This means that the acetoxyl group in the C-3 carbon in compound II and the corresponding hydroxyl groups in the molecule of staxybotrilactam A and the acetoxyl group in the monoacetate molecule **II** have an a-axial spatial configuration.

These data are also confirmed by the spectral data of stachibotrilactam A ROESY shown in Figure 4. The detection of the YaEO effect between the methyl radical CH3-19 and H-8 protons in the molecule in the same spectrum allows the β-orientation of the methyl radical in space, as well as the direction α -orientation relative to C-8. (CH3-18) methyl group.

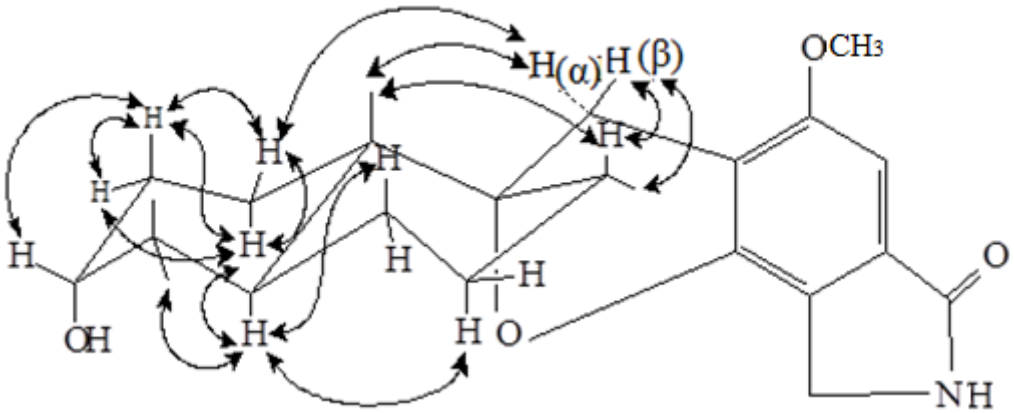

Figure 4. Conformation of the terpenoid portion of staxibotrilactam A (I) and the ROESY spectrum obtained in deuteropyridine.

Observation of the effect of YaEO between antiperiplanar proton pairs H-1 α - H-2 β ва H-5 - H-6βin a stachibotrilactam molecule is a characteristic feature of the ROESY spectrum, consistent with the spatial location of the installed A and B rings. Thus, the experimental data presented allow us to conclude that staxybotrilactam has the structure described in formula A (I) (Figure 4).

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