NMR SPECTRA, STRUCTURE, AND STEREOCHEMISTRY OF GROSSHEIMIN

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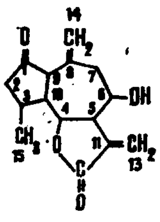
The sesquiterpene lactone grossheimin was first isolated from Grossheimia macrocephala (Muss.-Puschk.) Sosn. et Takht. [1]. Structure (I) was proposed as the most probable for it, since the position of the carbonyl remained unproven [2-3].

Spanish workers have shown by means of chemical transformations that the oxo group is located at C_2 and, having studied its stereochemistry, have established structure (II) for grossheimin [4, 5]. The present paper gives the results of a study of the NMR spectra of grossheimin and its derivatives, which confirm structure (II).

In the NMR spectra of grossheimin and acetylgrossheimin, a signal with an area of two proton units at 2.52 ppm forming a doublet with a distance between the components of 7 Hz has previously remained unassigned. This signal is converted into a singlet when the signal of the H_9 proton (ν_{H_2} = 316 Hz) is irradiated with a strong radiofrequency field, from which it follows that both protons to which the signal at 2.52 ppm corresponds are present in the vicinal position to the H_9 proton and this, in its turn, shows that the carbonyl group is located at C_2.

The position of the carbonyl is also confirmed by the fact that in the double-resonance spectrum with irradiation of the signals of the protons of the methyl group there is a singlet of the H_3 proton at 2.35 ppm (which is probably the strong component of the doublet). The presence of protons of a methylene group at C_2 should undoubtedly lead to additional splitting of the signal of this proton.



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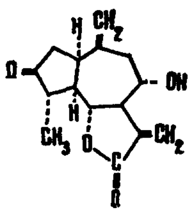

II

The parameters of the spectrum that have been obtained also permit the configuration and conformation of the grossheimin molecule to be determined. Below we give the chemical shifts and coupling constants of the protons of grossheimin. The spectrum was taken in $CDCl_3$ on an HA-100D spectrometer, the assignments and the values of δ and J being obtained by means of double resonance and by the INDOR method (see following page).

Lactone Ring

The presence of an exocyclic methylene group in the lactone ring leads to the situation that the atoms of the ring are present in a single (or almost a single) plane. Because of this, the dihedral angle between the H_5 and H_4 protons differs considerably from the angle of 180° for the trans linkage of the rings, while the angles for the protons located in the cis and trans position to one another will be less than 60° and more

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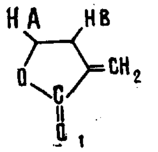
Protons	δ, ppm	J, Hz		
H_1, H_1'	2.52	$J_{1,9'} = 9$,	$J_{1,9'} = 3$	
H_3	2.35	$J_{3,10} = 9,5$	$J_{3,CH_3} = 7,0$	
H_4	4.0	$J_{4,10} = 9,5$,	$J_{4,5} = 8,5$	
H_5	2.25	$J_{5,4} = 8,5$	$J_{5,13'} = 3,0$	$J_{5,6} = 9,5$
			$J_{5,13} = 3,5$	
H_6	4.0	$J_{6,7e} = 6,3$	$J_{6,7a} = 10,0$	
H_{7a}	2,50	$J_{7a,6} = 10,0$	$J_{7a,7e} = -12,5$	
H_{7e}	2.98	$J_{7e,6} = 6,3$	$J_{7e,7a} = -12,5$	
H_9	3,16	$J_{9,1} = 9,0$	$J_{9,1'} = 3,0$	$J_{9,10} = 8,0$
H_{10}	2.3	$J_{10,3} = 9,5$	$J_{10,4} = 9,5$	$J_{10,9} = 8,0$
H_{13}	6.45	$J_{13,5} = 3,0$	$J_{13,13'} = -1,5$	
$H_{13'}$	6.65	$J_{13',5} = 3,5$	$J_{13',13} = -1,5$	
H_{14}	4,75	$\sum J = 1,4$		
$H_{14'}$	5,04	$\sum J = 1,9$		
CH_3	1.30	$J_{CH_3,3} = 7,0$		

than 180°, respectively. On the basis of the Karplus relation [6, 7] such changes must lead to the equalization of the values of the vicinal coupling constants of the protons of the lactone ring present in the cis and trans positions relative to one another.

According to the literature [8, 9], the following relation exists between the constants J_{cis} and J_{trans}: $J_{cis} \leq 8\text{-}9 \leq J_{trans}$. Another criterion for determining the method of attachment of the lactone ring may be the value of the change in the coupling constant between the H_A and H_B protons on passing from lactone with a vinyl group [1] to hydrogenated lactones [2]:



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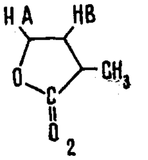


2

In lactones of type 2, the carbon atom bearing the methyl group is not in sp^2 hybridization, as in lactone of type 1, but in sp^3 hybridization. Consequently, the lactone ring in 2 is less strained than in 1. Hence, the dihedral angle between the A and B protons must be closer to 180° in 2 than in 1 if the protons are in the trans position to one another and closer to 60° if the protons A and B are in the cis position. According to the Karplus relation, on passing from 1 to 2 the constant J_{trans} should increase and J_{cis} should decrease.

In tetrahydrogrossheimin the constant $J_{4,5}$ is 1 Hz greater than in grossheimin, which shows the trans-configuration of the lactone ring.

The coupling constants between the H_4 and H_{10} and between the H_5 and H_6 protons possess a large value (about 10 Hz), which shows the trans position of the corresponding pairs of protons in relation to one another. On the basis of the values of the coupling constants $J_{6,7e}$ = 6.3 Hz and $J_{6,7a}$ = 9.5 Hz it is possible to evaluate the dihedral angle between the H_6, H_{7e}, and H_{7a} protons.

The coupling constants of the H_6 protons with the protons of the methylene group and the dihedral angle θ between them are connected according to the Karplus relationship by the relations

$$J_0 \cos^2 \theta = 6.3,$$
$$J_\pi \cos^2 (120 + \theta) = 9.5.$$

The ratio J_π/J_0 is usually 1.2. The solution of this system of equations gives the value θ = 37°.

Linkage of the Five- and Seven-Membered Rings

As is shown by the results of a study of molecular models and the stereochemical relationships of the vicinal and allyl constants, information on the linkage of the five- and seven-membered rings can be obtained by an analysis of the values of $J_{7,14}$ and $J_{9,10}$. The dihedral angle between the H_9 proton and the

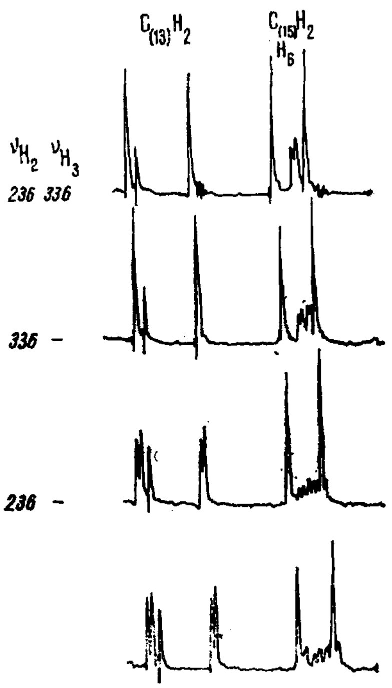


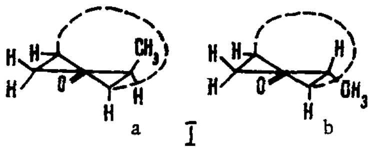
Fig. 1. Fragments of the NMR double- and triple-resonance spectrum of acetylgrossheimin.

double bond remains between 0 and 30° with both cis and trans linkage of the rings. Consequently, the allyl constant $J_{9,14}$ provides no information on the method of linkage of the ring. With the trans linkage of the rings, the dihedral angle between the H_{7e} proton and the plane of the double bond approximates to 90°. Consequently, the angle between the H_{7a} proton and the double bond approximates to 150°. With the cis linkage of the rings, the dihedral angles between the H_{7e} and H_{7a} protons and the plane of the double bond will be 140 and 20°.

On considering the stereochemical relationships of the allyl constants for the values of the dihedral angles given above, it can be seen that one must expect a larger value of $J_{14,7e}$ than of $J_{14,7a}$ when the rings have a trans linkage. In the case of a cis linkage of the rings, the ratio between the values of these constants is the opposite. The half-widths of the signals of both protons of the vinylmethylene group are approximately the same (2 and 2.5 Hz). The signals of these protons are in the form of broadened singlets. The broadening due to the nonuniformity of the magnetic field, determined from the chloroform signal, is 0.6 Hz. Thus, the broadenings of the signals of the protons of the vinylmethylene group due to the coupling of the protons of this group with one another and also with the allyl protons are 1.4 and 1.9 Hz. The contribution of the allyl protons to the broadening of the signals was determined by means of double resonance. A fall and an increase in the intensity of the signals of the vinylmethylene protons (Fig. 1) took place to a considerably greater extent on irradiation with a strong radiofrequency field of the H_9 and H_{7a} protons than with the irradiation of the H_{7e} proton. It follows from this that the allyl constant $J_{14,7e}$ is extremely small. Consequently, the five- and seven-membered rings possess the cis linkage. The vicinal constant $J_{9,10}$ found by means of the INDOR method has a value of 8.0 Hz. On using the stereochemical relationship [10], the following values of the dihedral angles are obtained: for cis protons 35° and for trans protons 136°. The latter corresponds to a shielded conformation of the cyclopentanone ring, which is energetically unfavorable. Because of this, the assignment of the observed coupling constant to cis protons is preferable.

Configuration of the Methyl Group

In determining the configuration of the methyl group, there are four probable variants of the mutual orientation of the methyl group and of the H_{10} proton (the "half-chair" conformation of the cyclopentanone ring is considered, which, as will be shown below, is indicated by the experimental results):



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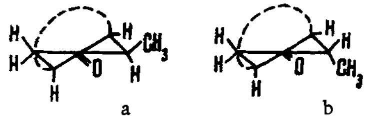


II

In the spectrum of a solution of grossheimin in a mixture of pyridine and benzene it is possible to distinguish the signals of the H_9 and H_{10} protons (Fig. 2), which enables us to find the coupling constants of these protons with the vicinal protons. The $J_{3,10}$ constant is determined directly from the spectrum of the H_{10} proton and is 9.5 Hz. However, the strong overlapping of the signals of the protons of the methylene group (the outer components of the quartets have a very low intensity in comparison with the inner ones) does not permit the differences (8 and 4.5 Hz) between the components of the signal of the H_9 proton to be equated with the $J_{1,9}$ and $J_{1',9}$ constants. The spectrum of the methylene protons is not a doublet (as in the

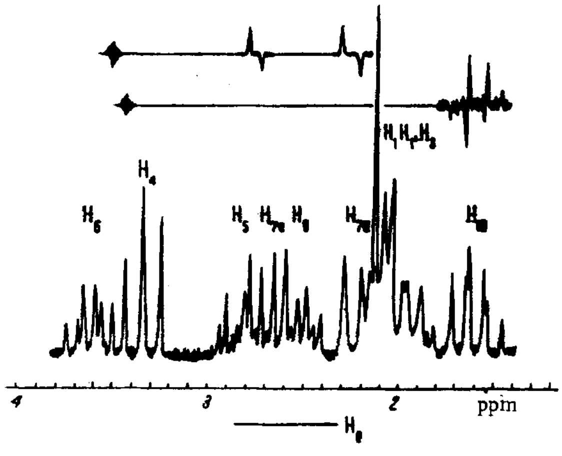


Fig. 2. Fragment of the monoresonance NMR spectrum and of the INDOR spectrum of grossheimin in a mixture of pyridine and benzene.

spectrum of grossheimin in chloroform); this shows that the chemical shift between the signals of the methylene protons is not much less than the coupling constant between them. Furthermore, the absence of strong outer lines in the spectrum of the methylene protons shows that the coupling constant between them is not much less than the chemical shift. Thus, the chemical shift between the methylene protons and the $J_{1',1}$ coupling constant are approximately equal to one another. Calculations performed with values of J characteristic for geminal constants between the protons of a methylene group present in the α position to a carbonyl (−16 to −18 Hz) in cyclopentanone rings [11] and the equality $\Delta\nu_{1',1} = J_{1',1}$ show that the best correspondence of the calculated values with the observed spectrum is achieved with coupling constants of the methylene protons with the H_9 protons of 3 and 9 Hz (the sum $J_{1,9} + J_{1',9} = 12$ Hz and is determined directly from the spectrum of the H_9 proton). The results of a measurement of the dihedral angles between the protons of the cyclopentanone ring in states Ia-IIb and the stereochemical relationship of the vicinal constant permit an unambiguous assignment of the coupling constants obtained to be made: 3 Hz to the trans protons and 9 Hz to the cis protons. The low value of the transoid constant shows that the cyclopentanone ring is present in state I. For this state large values both of the cisoid and of the transoid $J_{3,10}$ coupling constants must be expected, which does not permit the configuration of the methyl group to be determined from the value of this constant.

It can be seen from a consideration of molecular models that if the methyl group or the proton at C_3 is located on the same side of the plane of the molecule as the lactone proton it is spatially close to the latter. Because of this, a considerable Overhauser effect on the signal of the lactone proton on the irradiation of the protons of the methyl group or the H_3 proton with a strong radiofrequency field is possible. An experiment to detect the Overhauser effect was performed for solutions of grossheimin in a mixture of pyridine-d_5 and benzene-d_6, in which the signal of the lactone proton remains separate from the signal of the hemihydroxyl proton. The intensity of the signal of the lactone proton increased by 20% when the H_3 proton was irradiated with a strong radiofrequency field. When the protons of the methyl group were irradiated with a H_2 field, no increase in the area of the lactone signal was observed. It follows from this that in grossheimin the methyl group and the lactone proton are on different sides of the plane of the molecule.

Conformation of the Cyclopentanone Ring

In condensed systems, as experimental results show [12, 13], the cyclopentanone ring assumes the half-chair or the envelope conformation. A distinguishing feature of the former is that the two carbon atoms in the β positions to the carbonyl are located on different sides of the plane passing through the $-C-\underset{\displaystyle O}{\overset{}{\underset{\|}{C}}}-C-$ atoms. Their distances from this plane are the same.

In the envelope conformation, four carbon atoms including the carbon of the carbonyl group are located in one plane, and the fifth is above or below this plane.

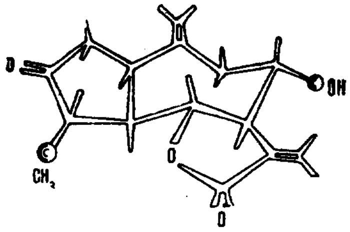
Each of the two conformations has different values of the dihedral angles between the protons or the substituents in the ring. In determining the dihedral angles between the protons of the cyclopentanone ring we made use of the Karplus relation with the Bather-By [10] coefficients, which were found in an analysis of a large number of vicinal constants:

$$^3J = 7 - \cos\theta + 5\cos 2\theta.$$

According to this relation, for the constants $J_{9,10}$ = 8 Hz, $J_{1,9cis}$ = 9 Hz, $J_{1,9trans}$ = 3.5 Hz, and $J_{3,10}$= 9.5 Hz, the values of the dihedral angles are, respectively, 35, 27, 105, and 145°. The latter corresponds to a dihedral angle between the methyl group and the H_{10} proton of 25°.

The closeness of the dihedral angles between the cis $H_{1,9}$ protons and also between the methyl group and the H_{10} proton shows that the cyclopentanone ring possesses the half-chair conformation, and the values of the other dihedral angles agree well with this.

On the basis of the facts presented, a perspective formula for grossheimin has the following form:



Perspective formula of the grossheimin molecule.

SUMMARY

1. The chemical shifts and coupling constants of all the protons in the grossheimin molecule have been found with the aid of double and triple resonance and also by the INDOR method.

2. The position of the oxo group at C_2 in grossheimin has been confirmed.

3. The configuration and conformation of the grossheimin molecules have been determined.

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