THE STRUCTURE OF BADKHYSININ

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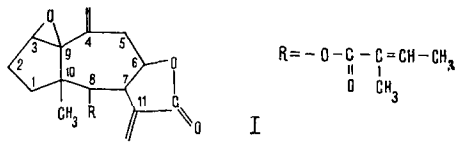
In a chemical investigation of the sesquiterpene lactone badkhysinin isolated from the resin of the roots of Ferula oopoda (Boiss et Buhse) Boiss., four possible structures were proposed [1]. Further work [2] based on a partial interpretation of the NMR spectra both of this lactone and of its derivatives recorded on a spectrometer with a resolving capacity of 60 MHz, taking the results of a chemical study into account, permitted the probable structure (I) to be put forward for badkhysinin.



I

The selenium dehydrogenation of badkhysinin derivatives previously reduced with $LiAlH_4$ led to the formation of chamazulene. This fact made it possible to suggest that the compound under consideration was based on a guaiane carbon skeleton. However, the detection in its NMR spectrum (Fig. 1, curve a) of the singlet of an angular methyl group (0.84 ppm, $CH_3-\overset{|}{\underset{|}{C}}-$) shows that this compound belongs to the pseudoguaianolide group.

The present paper gives the results of a revision of the structure of badkhysinin. As shown previously [1, 2], the substance contains an oxide ring, as is confirmed by the formation of hydroxy derivatives in the exhaustive hydrogenation of badkhysinin. According to structure (I), the oxide ring in the molecule of the substance is present on secondary and tertiary carbon atoms. Consequently, the area of the signal of the proton(s) of the epoxy group should correspond to one proton.

The area of the signal at 3.65 ppm corresponding to protons in an oxide ring is equal to two proton units. Consequently, the epoxy group is located on secondary carbon atoms. Furthermore, in the NMR spectrum there is a doublet at 2.25 ppm (1H, J=10 Hz), whose components are split additionally, apparently through long-range spin–spin coupling with the protons of an exocyclic methylene group at C_1. Structure (I) lacks a proton which could give such a J constant. It might be assumed that the oxide ring is present at C_2-C_3, and H_3, interacting with one neighboring proton (H_3), gives a doublet signal. However, the value of J excludes this possibility. The spectrum shows the signal of a lactone proton – a quartet at 4.87 ppm (J_1=10 Hz; J_2=7.5 Hz). The nature of the splitting of this signal shows that there are two protons adjacent to the lactone proton.

The facts given show that badkhysinin is a sesquiterpene lactone based on the eudesmane, and not the pseudoguaiane, carbon skeleton. As already mentioned, the NMR spectrum of badkhysinin has one singlet characteristic for an angular methyl group. In view of this, it is possible to answer the question of the nature of the remaining double bonds. The substance contains three double bonds, two of which relate to exocyclic methylene groups. The protons of a methylenic double bond conjugated with the carbonyl of the lactone ring show two doublets of the $>C=C\langle^{H}_{H}$ group with centers at 5.54 (J=4 Hz, 1H) and 6.29 ppm

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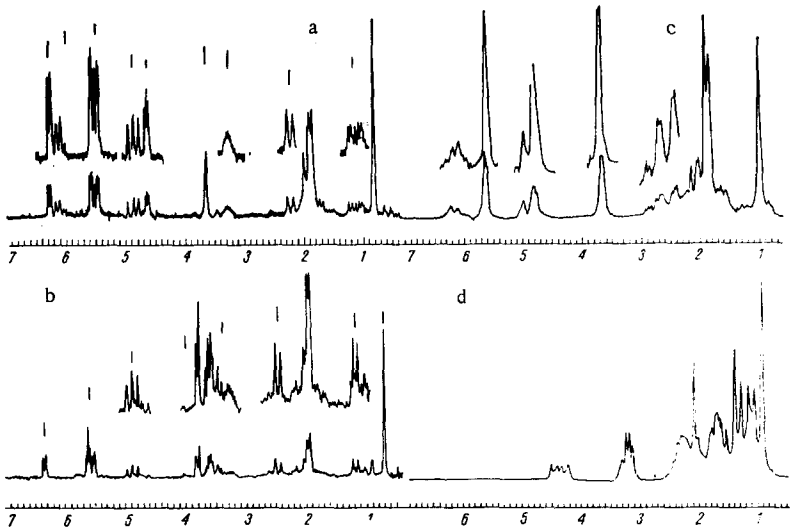

Fig. 1. NMR spectra of badkhysinin (a), saponified badkhysinin (b), isobadkhysinin (c), and the keto epoxy lactone with mp 179-180°C (d).

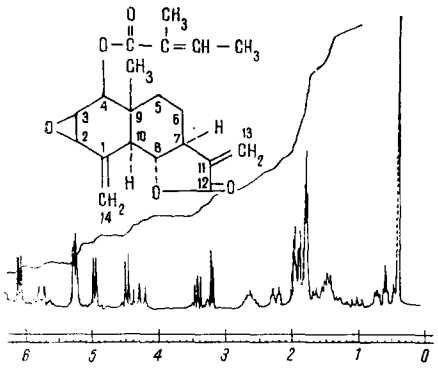

Fig. 2. NMR spectrum of badkhysinin in benzene solution.

(J = 4 Hz, 1H). Two doublets at 5.47 (J = 2 Hz, 1H) and 5.59 ppm (J = 2 Hz, 1H) also relate to a $\rangle C=C\langle^{H}_{H}$ group at C_1. The third double bond is present in a side chain. This is confirmed by the saponification of badkhysinin with alkalis. This gave a hydroxy epoxy lactone $C_{15}H_{18}O_4$ with mp 185-186°C and an acid whose IR spectrum coincided accurately with that of tiglic acid [3]. In the spectrum of badkhysinin, the vinyl methyl groups of the tiglic acid residue appear in the form of a multiplet at 1.80-2.10 ppm. A one-proton multiplet at 6.15 ppm, caused by the vinyl proton of the ester group, is partially superposed on a doublet of an exocyclic methylene group in the lactone ring (6.29 ppm). The fact that these signals relate to the ester group is shown by the NMR spectrum of the saponified product (Fig. 1b), which does not contain these signals.

It is known that benzene has a tendency to form molecular complexes with molecules having centers of partial positive charge [4]. Taking this into account, we recorded the NMR spectrum of badkhysinin in benzene solution.

In this NMR spectrum (Fig. 2), there are considerable shifts in the proton resonance signals as compared with the spectrum taken in $CDCl_3$ solution (Table 1), which likewise enables the structure of the individual signals to be considered. The two protons in the oxide ring appear in the form of a doublet (H_2, $\delta = 3.25$ ppm, $J = 3$ Hz) and a quartet (H_3, $\delta = 3.43$ ppm, $J_1 = 5$ Hz, $J_2 = 3$ Hz). The doublet with its center at 4.49 ppm (J = 5 Hz) relates to a proton in an ester group. The spin-spin coupling constant of this proton (5 Hz) shows its interaction with H_3. Consequently, the ester group is probably located at C_4.

The double bond in the methylene group of the lactone ring readily migrates into the ring during hydrogenation. Such migration takes place mainly during the reduction of this bond in ethanol using as catalyst Pt (from PtO_2) and deactivated Raney nickel. The phenomenon mentioned is characteristic not only for badkhysinin but also for some other lactones [5-8].

The NMR spectrum of isobadkhysinin (Fig. 1c), $C_{20}H_{24}O_5$, mp 182-183°C, lacks the doublets caused by the protons of the $\rangle C=C\langle^{H}_{H}$ group attached to the lactone ring. This could be explained by the assumption that during the hydrogenation of one double bond in the presence of deactivated Raney nickel it

TABLE 1

Compound	Solvent	CH_3 at C_{-9}	CH_3 of an ester group	-CHOf an ester group	Protons on C									
					2	3	4	7	8	10	13	14		
Badkhysinin	$CDCl_3$	0,84, s*	1,85, t 1,95 d/t J=7 Hz	6,15, m	3,65, d J=2 Hz	3,65, d J=2 Hz	4,65, m	3,27, m	4,87, q J_1=10 Hz J_2=7,5 Hz	2,25 d/t J=10 Hz	6,29, d J=4 Hz 5,54, d J=4 Hz	5,47, d J=2 Hz 5,59, d J=2 Hz		
The same	C_6H_6	0,40, s	1,80, t 1,92 d/t J=7 Hz	5,78, m	3,25, d J=3 Hz	3,43, q J_1=5 Hz J_2=3 Hz	4,49, d J=5 Hz	2,64, m	4,31 q J_1=10 Hz J_2=8 Hz	2,25 d/t J=10 Hz	6,12, d J=4 Hz 4,98, d J=4 Hz	5,26, d J=2 Hz 5,29, d J=2 Hz		
$\Delta\delta = \delta_{CDCl_3} - \delta_{C_6H_6}$		0,44	0,05 0,03	0,37	0,40	0,22	0.16	0,63	0,56	0	0,17 0,56	0,21 0,30		

*s – singlet; d – doublet; t – triplet; q – quartet; d/t – doublet each component of which consists of a triplet; m – multiplet.

was this double bond that was hydrogenated. Consequently, the spectrum should exhibit a three-proton doublet of a $CH_3-CH<$ group, but this is not the case. In contrast to this, the area of the vinyl methyl signals at 1.7-2.1 ppm increases. Furthermore, the nature of the signal of the lactone proton changes. The H_8 signal appears in the form of a doublet partially superposed on the H_4 signal at 4.93 ppm (J=10 Hz).

The spectrum also shows the signals of an angular methyl group (singlet at 1.02 ppm), of the protons in an oxide ring (doublet with its center at 3.67 ppm, J=2 Hz), of H_4 (at 4.83 ppm), of an exocyclic methylene (at 5.65 ppm), and of the vinyl proton of an ester group (multiplet with a center at 6.15 ppm).

During hydrogenation in ethanol, in addition to the migration of the double bond into the lactone ring the oxide ring is opened. Only hydrogenation in ethyl acetate with a Pd/C catalyst causes the reaction to proceed in the direction of the formation of a saturated compound. It is important to note that in the latter the oxide ring is retained. Its saponification leads to the formation of a hydroxy epoxy lactone, $C_{15}H_{22}O_4$, with mp 204-205°C, the NMR spectrum of which shows a singlet characterizing a $CH_3-\overset{|}{\underset{|}{C}}-$ group (at 0.85 ppm) and doublets with centers at 1.20 ppm (J= 6 Hz) and 1.30 ppm (J= 7 Hz) caused by the presence of two $CH_3-CH<$ groups. The spectrum also shows the signals of the protons of an oxide ring (triplet at 3.30 ppm), in an OH group (3.40 ppm), and in a lactone ring (quartet at 4.30 ppm, J_1=10 Hz, J_2= 7.5 Hz). In the NMR spectrum of the oxidized product ($C_{15}H_{20}O_4$, mp 179-180°C) (Fig. 1d) the signal at 3.40 ppm (1H) is absent. The singlet of an angular methyl group is found at 1.00 ppm; $CH_3-CH<$ groups at C_1 and C_{11} appear in the form of doublets with centers at 1.15 ppm (J=6 Hz) and 1.40 ppm (J=7 Hz). The protons of the epoxy group form a quartet with its center at 3.30 ppm (2H). A quartet at 4.4 ppm (J_1=10 Hz, J_2=7 Hz) characterizes a lactone proton.

Since the intensity of the signal of the protons in the oxide ring is equivalent to 2H, the ring can be located only at C_2-C_3 or C_3-C_4. Usually, these protons are found in the spectrum at 3.42 ppm [9]. The signals relating to these protons in the spectra of badkhysinin, isobadkhysinin, and saponified badkhysinin are located in the comparatively weak field (by 0.23 ppm). Furthermore, the chemical shifts of the protons of the exocyclic methylene group at C_1 are also shifted downfield (by 0.59 ppm). This shows the propinquity of the groups considered. Consequently, the oxide ring is present at C_2-C_3. This point of view is confirmed by the chemical shift of saturated badkhysinin derivatives – the hydroxy epoxy lactone with mp 204-205°C and the keto epoxy lactone with mp 179-180°C (3.30 ppm).

The results of a comparative analysis of the spin–spin coupling constants of the lactone proton (H_8) and the neighboring protons (H_{10} and H_7) enable the stereochemistry of these centers to be determined. The NMR spectrum of badkhysinin has a one-

proton doublet (at 2.25 ppm, H_{10}) with a coupling constant of 10 Hz. The spin–spin coupling constant of this proton with the neighboring hydrogen atoms at C_8 (J = 10 Hz) shows their trans arrangement. The H_8 signal is split additionally because of interaction with the hydrogen at C_7 with a second splitting constant of 7.5 Hz. Thus, the protons in positions 8 and 7 must also be in the trans position. The values of the constants for spin–spin coupling between the H_8 and H_{10} protons (10 Hz) and the H_8 and H_7 protons (7.5 Hz) are similar to the values of the protons in similar positions in the badkhysinin molecules [10]. This suggests that the stereochemistries of badkhysin and badkhysinin at C_7, C_8, and C_{10} are similar.

Summarizing what has been said, it may be concluded that badkhysinin is the ester of 4-hydroxy-2,3-epoxyeudesma-1(14),11(13)-dien-8,12-olide and 1,2-dimethylacrylic acid.

EXPERIMENTAL

The NMR spectra of badkhysinin and the saponified product were recorded on a JNM-4H-100/100 MHz spectrometer and those of isobadkhysinin, the hydroxy epoxy lactone (mp 204-205°C), and the keto epoxy lactone (mp 179-180°C) on a JNM C-60 instrument. The NMR spectrum of badkhysinin in benzene was obtained on a Varian HA-100D spectrometer.

Deuterochloroform was used as the solvent. The chemical shifts are given in the δ scale, the internal standard having been tetramethylsilane.

SUMMARY

On the basis of NMR spectra, it has been shown that badkhysinin is a lactone of the eudesmane series and is the ester of 4-hydroxy-2,3-epoxyeudesma-1(14),11(13)-dien-8,12-olide and 1,2-dimethylacrylic acid.

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