NMR INVESTIGATION OF THE SPATIAL STRUCTURE OF QUINOLIZIDINE ALKALOIDS

IV.* CONFORMATION OF SOPHORIDINE IN SOLUTION

F. G. Kamaev, V. B. Leont'ev,
Kh. A. Aslanov, Yu. A. Ustynyuk,
and A. S. Sadykov

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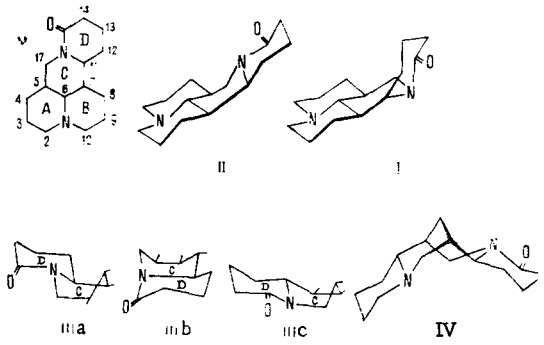
The structure of sorphoridine was first studied by F. Rulko and N. F. Proskurnina [2]. The "Bohlmann" absorption in the 2800-2700 cm^{-1} region in the IR spectra of sophoridine and the relative rates of dehydrogenation of matrine, allomatrine, and sophoridine over palladized asbestos and mercuric acetate enabled them to determine the spatial structure of sophoridine as A/B-, A/C-, B/C-trans, and C/D-cis. Subsequently, F. Rulko [3] established that sophoridine isomerizes over Pt into isosophoridine, which has the A/B- and A/C-cis, B/C- and C/D-trans configuration. A discussion of the mechanism of the isomerization of sophoridine over Pt/H_2 by other workers [4] showed that the cis addition of the catalyst with its subsequent migration may lead to the transformation of the conformation of the matrine system of the sophoridine type given by Rulko and Proskurnina [2] into the conformation with A/B-, A/C-cis and B/C-, C/D-trans.



II I

IIIa IIIb IIIc IV

On the basis of transformation of sophoridinic acid [5] and also of the IR spectrum of the methiodide of the reduced form of sophoridine [6], A. I. Begisheva, Kh. A. Aslanov, and A. S. Sadykov established that the C/D fragment of sophoridine has the syn-cis form, i.e., spatial structure I corresponds to this alkaloid. Thus, the conformation of sophoridine (I) logically satisified the physicochemical results obtained in a study of sophoridine derivatives.

In addition, D. Dzh. Kamalitdinov, S. Iskanderov, and S. Yu. Yunusov proposed the spatial structure II for dextrorotatory sophoridine on the basis of the fact that on the dehydration of sophoridine with mercuric acetate, like matrine and allomatrine (C/D-trans) it forms 5-hydroxy-6,7-dehydromatrine [7]. Furthermore, the same workers [8] additionally substantiated structure (II) by the fact that in the PMR spectra of sophoridine and its mono- and dichloro derivatives (at C_{14}) the signals of the protons at C_{11} and C_{17} in the weak-field region are absent. However, as will be shown below, the signals of the H_{17a} and H_{11} protons are in actual fact located in the weak-field region (2.92 and 3.33 ppm). It must be mentioned that structure (II) also satisfies the results of those chemical transformations of sophoridine which led to the proof of structure (I).

* For Communications I-III, see [1].

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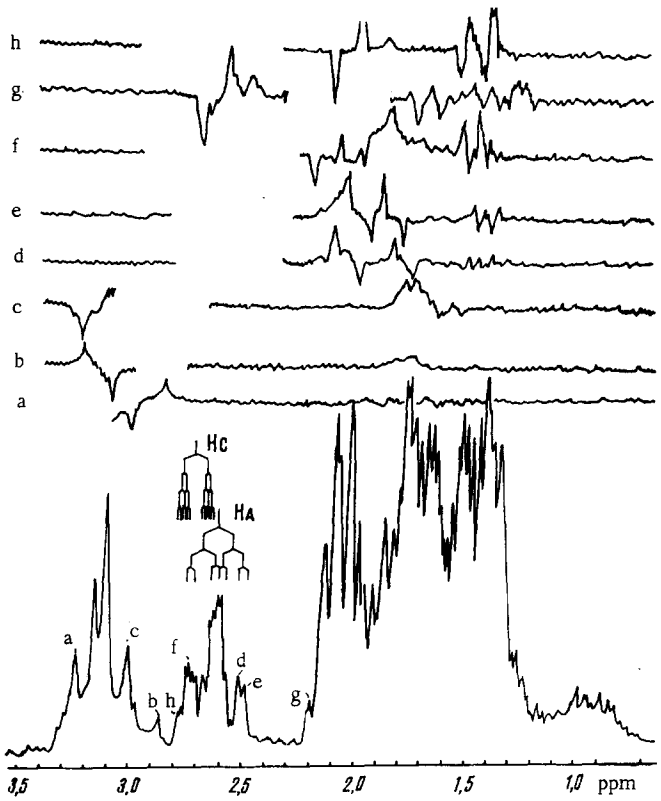


Fig. 1. PMR spectrum of sophoridine at a frequency of 100 MHz in CS_2 (a-h – INDOR experiments using the corresponding lines of the spectrum).

It may be assumed that the uncertainty in our ideas of the conformation of sophoridine is due to the fact that in solutions its molecule exists in a spatial form (different from I and II) which on interacting with the appropriate reagent forms the derivative described in the previous papers. This form must apparently be conformationally labile, which is partially ensured by the nitrogen atoms, which are capable of inversion. Consequently, the predominant conformation of sophoridine in solution must be established by methods not affecting the position of the conformational equilibrium.

The successful use of the INDOR method [9, 10] to interpret the PMR spectra of the quinolizidine alkaloids [1, 11] permitted us to hope that it would provide the possiblity of obtaining unambiguous information on the conformation of sophoridine. In actual fact, from the PMR spectra of sophoridine we have determined the required spin–spin coupling constants and chemical shifts on the basis of which we have reconsidered the conformation of this compound.

The PMR spectrum of sophoridine (Fig. 1) differs from the spectra of all the other alkaloids of the matrine series by the absence of a resonance signal of the H_{17e} proton in the 4.0-4.5 ppm region. This means that the H_{17e} proton does not lie in the nodal plane of the lactam carbonyl at C_{15}.* An analysis of molecular models has shown that for the two proposed spatial structures of sophoridine, I and II, the H_{17e} proton must be present in the nodal plane of the lactam carbonyl and because of this they can both be rejected. In Fig. 1, a complex multiplet with an integral intensity corresponding to three protons is observed in the 2.85-3.35 ppm region. The INDOR experiments a-c (see Fig. 1) with the recording of the intensity of the lines of this multiplet permit the conclusion that two protons interact with one another with $J = 13.6$ Hz. The minimum number of spin–spin interactions and the location of the signals in weak fields shows that the lines found belong to the H_{17e} and H_{17a} protons. In order to determine the parameters of the signals accurately, we recorded the PMR spectra of sophoridine at a frequency of 300 MHz in CS_2, C_6H_6, and $CS_2+C_6H_6$

*A paramagnetic shift of the resonance signal of the equatorial proton in the β position to the carbonyl is observed both for cis- and for trans-quinolizidines if this proton is in the nodal plane of the carbonyl [1, 8, 11, 12]. The question of the influence of the orientation of a lactam carbonyl on the chemical shifts of neighboring protons is discussed in detail by Cahill and Crabb [13].

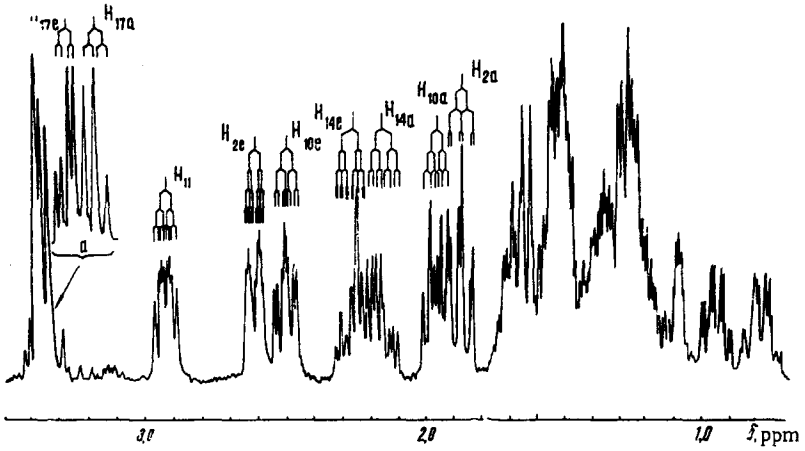


Fig. 2. PMR spectrum of sophoridine at a frequency of 300 MHz in benzene (a – signals of the H_{17e} and H_{17a} protons in the solvent system $CS_2+C_6H_6$).

(1:1). The most informative in the absence of experiments on double resonance proved to be the spectrum in benzene, which is given in Fig. 2. The increase in the resonance frequency and the effect of the solvent enabled the signals of the three protons located in weak fields to be separated. In Fig. 2a (solution in $CS_2+C_6H_6$) it can be seen that the H_{17e} and H_{17a} signals form the AB part of a ABX spin system with the following constants: $J_{17e,17a}=13.6$ Hz, $J_{17e,5}=4.9$ Hz, and $J_{17a,5}=11.2$ Hz. It follows from the values of the spin–spin coupling constants that the H_5 proton is axial with respect to ring C. In benzene the signal of the tertiary H_{11} proton is shifted by 0.2 ppm upfield as compared with the corresponding signal in CS_2 [14] and is located at 2.92 ppm. The width of the signal ($\delta\nu=22.8$ Hz) shows the trans linkage of rings C and D. For comparison, we may mention that in the spectra of matrine and allomatrine (C/D-trans) the widths of the H_{11} signals are 23.3 and 24 Hz, respectively [11, 12].

While in all matrine alkaloids the difference in the chemical shifts of H_{17e} and H_{17a} is between 1 and 2 ppm, in sophoridine this difference is 0.17 ppm in carbon disulfide and less than 0.1 ppm in benzene. This is possible only if the angles of the $C_{17}-H_{17e}$ and $C_{17}-H_{17a}$ bonds with the nodal plane of the lactam carbonyl are approximately equal. The position of the nodal plane of the carbonyl group between the geminal protons at C_{17} is possible only with a specific distortion of ring C or ring D.* Ring D is external and is linked with ring C at two points, and therefore it must adopt an energetically favorable conformation ("flat chair"), which is the same for all the matrine alkaloids. In the spectrum of sophoridine (see Fig. 2), in the 2.1-2.33 ppm region there are the signals of H_{14e} and H_{14a}, identified through the geminal constant $J=17.0$ Hz, the value of which is due to a π contribution of the neighboring carbonyl group [15]. The presence in the H_{14e} spectrum of a long-range spin–spin coupling constant, $J=1.1$ Hz, with the H_{12e} proton ("W" rule) confirms that the conformation of ring D is the flat chair conformation. Ring C is linked with rings A, B, and D at five points out of six and it is just here that the distortion of the chair conformation must be sought.

The "boat" conformation possesses a lower order of symmetry, and the presence in ring C of a heteroatom and of the neighboring rings creates the possibility for the existence of at least three nonequivalent conformations of this ring in the boat form. In a structure of the C/D fragment of type (IIIa), which has been proposed previously for the conformation of (II) [7], with the N_{16} and C_6 atoms at the "bows" and "stern", the H_{17e} proton is in the plane of the lactam and must resonate in the 4.0-4.5 ppm region, as is observed in the PMR spectrum of 15-oxospartein (IV), which has an analogous fragment [16]. The same can be said about structure (IIIc), which has the C_{17} and C_7 carbons at the bow and stern. The arrangement of the angular plane of the carbonyl group between the H_{17e} and H_{17a} protons is realized in conformation (IIIc), where the tertiary carbons C_5 and C_{11} are at the bow and stern. Thus, on the basis of the stereospecific influence of the orientation of the carbonyl group and the close values of the chemical shifts of the H_{17e} and H_{17a} signals, the conformation of the C/D fragment of sophoridine can be represented by form (IIIc).

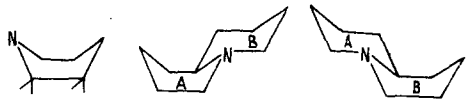
In the spectrum of sophoridine (see Fig. 2), there are the signals of two protons in the 2.43-2.66 ppm region. In the PMR spectra of quinolizidine derivatives equatorial protons present in the α position to the

*The absence of a temperature dependence of the parameters of the spectra of matrine (trans-quinolizidone), 17-oxospartein (cis-quinolizidone), and sophoridine in the range of temperatures from –90 to +190°C witnesses the presence of one predominant conformation of these bases in solution.

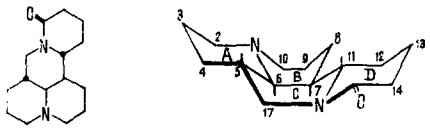
nitrogen generally resonate in this region [17, 18]. The signal of one of them at 2.61 ppm is split by the geminal proton (J = 11.4 Hz) and by several small spin–spin coupling constants, and from its multiplicity it corresponds to the signal of an ordinary equatorial proton. The other signal is located at 2.51 ppm and is split by spin–spin couplings with constants of 11.2, 9.2, and 3.8 Hz, and in its multiplicity it is similar to an axial α proton. The INDOR experiments d-h with the recording of the intensities of the lines of these protons (see Fig. 1) permit the conclusion that these two protons (H_A and H_C) are not bound by a spin–spin interaction and, consequently, are located on different α-carbon atoms – C_2 and C_{10}.

It must be mentioned that in the PMR spectra of the matrine alkaloids containing an A/B-trans-quinolizidine system the signals of the H_{2e} and H_{10e} protons have the same multiplicity and practically identical values of the chemical shifts, in spite of the different nature of the spatial structures of the C/D moieties [1, 11]. The stable "Bohlmann" band in the IR spectrum of sophoridine [2] indicates the trans-linkage of rings A and B fairly reliably; nevertheless, the two α protons in the 2.43-2.66 ppm region have not only different values of the chemical shifts but also different multiplicities. This is apparently connected with a difference in the conformations of rings A and B. To investigate this hypothesis, it is necessary to determine the multiplicities of the signals of the axial α protons geminal to the H_{2e} and H_{10e} protons found previously.

The signals of the H_{2a} and H_{10a} protons are located in the 1.8-2.04 ppm region (see Fig. 2). To a first-order approximation, the signal of one of them at 1.98 ppm is split with constants of 11.2, 7.4, and 7.4 Hz, and the signal of the other proton, at 1.89 ppm, with constants of 11.4, 11.4, and 2.7 Hz. Since the small difference in the geminal constants (11.4 and 11.2 Hz) does not give confidence in the separation of the H_{2a} and H_{10a} signals, we returned once more to double-resonance experiments. The INDOR experiments d-h with the recording of the intensity of the lines of the H_A signal (see Fig. 1), and also control experiment g show that the geminal partner of the H_A proton is located in a weaker field than the other axial α protons (see Fig. 1h). The separation of the signals made on the basis of the INDOR experiments permits the conclusion that the signals at 2.61 and 1.89 ppm (see Fig. 2) form a geminal pair of α protons the multiplicity of which corresponds to the multiplicity of the equatorial and axial α protons in the "chair" conformation of the ring. From the Karplus dependence of the vicinal spin–spin constants on dihedral angles [19], it follows that the multiplicity and the similarly large (25-26 Hz) widths of the signals of the other geminal pair of α protons are characteristic for the "boat" conformation (type V) of that ring in which these protons are located. Since the boat–chair trans-linkage of two rings is possible in two ways, the conformation of the A/B fragment of the sophoridine molecule can be represented as (VIa) or (VIb).



V VIa VIb



VII

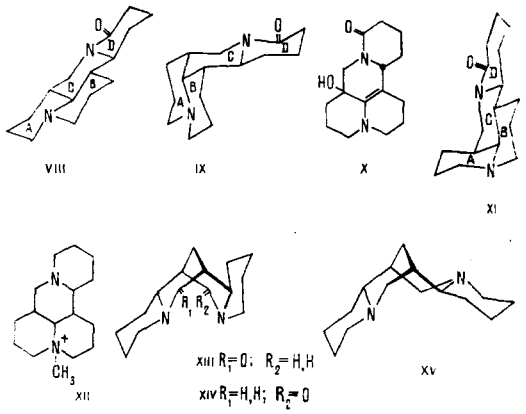
The conformation of the C/D fragment of the sophoridine molecule was determined above as (IIIc). The combination of the A/B and C/D fragments in conformations (VIa) and (IIIc) is sterically impossible, and the formation of the sophoridine molecule takes place by the linkage of fragments (VIb) and (IIIc) by equatorial bonds at the C_5, C_6, and C_7 carbon atoms. Thus, the conformation of the sophoridine molecule (VII) has been determined as A/B-, A/C-, and C/D-trans, B/C-cis, with the chair conformation for rings A and D and the boat conformation for rings B and C.

The definitive assignment of the signals in the PMR spectrum of sophoridine for conformation (VII) is shown in Fig. 2. It must be mentioned that with the nondistorted "boat" conformation (V), the nature of the splitting of the signals of the geminal α protons must be the same. The different natures of the multiplicities of the H_{10e} and H_{10a} signals is apparently explained by some distortion of rings B from the classical "boat" form, and also by different degrees of influence of the unshared pair of electrons of the N_1 nitrogen on the vicinal spin–spin interactions [20] in which these protons participate.

The results of a study of the ^{13}C spectrum of sophoridine confirm conformation (VII). In all the spectra of the matrine alkaloids (A/B-trans), the chemical shifts of C_2 and C_{10} differ by not more than 0.3 ppm

[21]. A similar situation should be observed for conformations (I) and (II). However, in the spectrum of sophoridine the difference in the chemical shifts of C_2 and C_{10} amounts to 5.8 ppm, which is due to the different forms of rings A and B.

Conformation (VII) determined by the NMR method corresponds to results obtained previously on the chemical transformations of sophoridine [2-8]. It is known that matrine isomers containing a large number of cis-hydrogen atoms react faster on dehydrogenation over palladized asbestos or mercuric acetate [22, 23]. It has been established [2] that sophoridine dehydrogenates faster than allomatrine (VIII) but slower than matrine (IX). Since there are three cis-hydrogens in matrine (H_5, H_6, and H_7), while in allomatrine there are none, there must be two cis-hydrogens in the sophoridine molecule. The cis-oriented H_6 and H_7 hydrogens in the conformation of (VII) satisfy this condition. On dehydrogenation with mercuric acetate, matrine, allomatrine, and sophoridine form one and same dehydro product – 5-hydroxy-6,7-dehydromatrine (X) [22, 23]. On the addition of a hydroxy group to C_5 and on the introduction of a double bond just in position 6,7 the differences in the conformations of the molecules (VII-IX) are eliminated and, as a consequence, the same molecule (X) is formed.



On isomerization over Pt, sophoridine passes into isosophoridine (XI), the molecule of which contains a A/B-cis-quinolizidine system [3, 4]. In the conformation of sophoridine (VII), two cis-hydrogens (H_6 and H_7) ensure the direct formation of isosophoridine (XI) in almost 100% yield.

The reduction of sophoridine methiodide gives sophoridine monomethiodide (XII), the IR spectrum of which lacks absorption in the 2800-2700 cm^{-1} region [6]. This has permitted one of us to suggest the cis-linkage of rings C and D in the sophoridine molecule. The absence of a "trans" band in the spectrum of (XII) can be explained by the possible isomerization of the C/D fragment in the reduction reaction. For example, the reduction of aphylline (XIII) and of 17-oxospartein (XIV) forms sparteine (XV) [24], differing from (XIII) and (XIV) by the conformation of ring C and by the type of linkage of rings C and D. In view of this, to continue this work it is necessary and of interest to study the conformations of sophoridine derivatives.

EXPERIMENTAL

The PMR spectra were recorded on Varian HA-100D, XL-100, and HR-300 spectrometers.* The samples were in the form of 15% solutions of sophoridine (by weight) in CS_2 and C_6H_6, and in a mixture of these solvents. The INDOR experiments were performed on the HA-100D instrument. The chemical shifts are given in the δ scale relative to HMDS. The samples of sophoridine were kindly given to us by A. I. Begisheva.

SUMMARY

On the basis of PMR spectra at 100 and 300 MHz, the conformation of the molecule of the alkaloid sophoridine in solution has been determined as A/B-, A/C-, and C/D-trans, B/C-cis, with the "chair" conformation of rings A and D and the "boat" conformation of rings B and C.

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*The spectra at a frequency of 300 MHz were taken by Lou Kéri (Varian, USA).

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