MASS SPECTRA OF ALKALOIDS OF THE TYPE OF SONGORINE

Structure of Songoramine

M. S. Yunusov, Ya. V. Rashkes, S. Yu. Yunusov, and A. S. Samatov

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In the separation of the total alkaloids of the tubers of Aconitum karakolicum collected in the upper reaches of the Tyup River (Terskei Ala Tau range), we isolated aconitine, songorine, and an alkaloid with mp 211–212° C [1]. The isolation of the latter from Aconitum soongoricum Stapf. has been reported previously. On the basis of an elementary analysis, the composition $C_{22}H_{31}O_3N$ was proposed for the alkaloid. However, the molecular weight determined mass-spectrometrically showed that this base contains two hydrogens less, $C_{22}H_{29}O_3N$. The IR spectrum of the alkaloid shows absorption bands at 1722 cm^{-1} ($\nu_{C=O}$), 1660 cm^{-1} ($\nu_{C=C}$), and 3400 cm^{-1} (OH or NH group). The UV spectrum has an absorption maximum at 295 mμ (log ε 2.60), which is characteristic for β,γ-unsaturated ketones. The NMR spectrum shows the presence of a tertiary methyl group (0.79; singlet), an ethyl group (0.97; triplet), and a terminal methylene group (5.15 and 5.23, singlets). The IR spectrum of the base is similar to that of songorine (I).

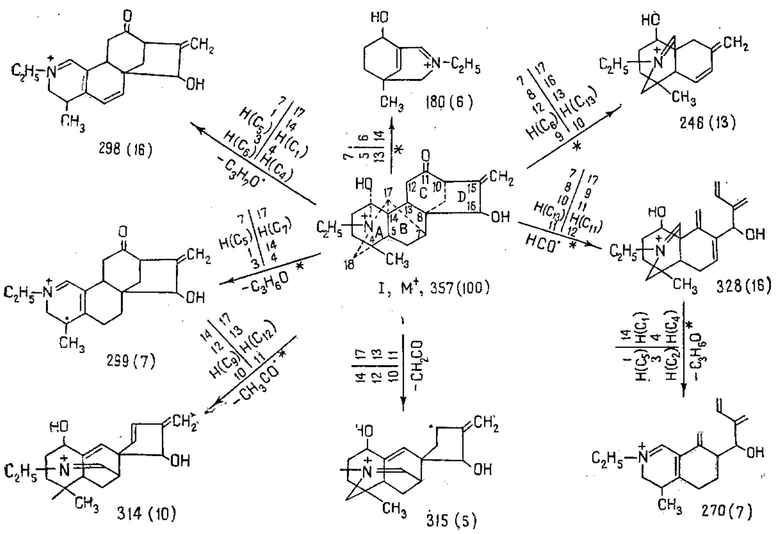
The acetylation of the base gave a substance containing two O-acetyl groups. Hydrogenation over platinum led to a tetrahydro derivative. The IR and NMR spectra show the absence from the product obtained of a terminal methylene group and the appearance of a secondary methyl group (0.75; J = 7 Hz, doublet). In the IR spectrum the $\nu_{C=O}$ absorption band in the IR spectrum had shifted to 1690 cm^{-1}. A similar shift is observed in passing from songorine to dihydrosongorine (II), which proved to be identical with the tetrahydro derivative of this base, which we have called "songoramine."

In view of the similarity of songoramine and songorine, we have studied the mass spectra of songorine and dihydrosongorine and their diacetates, N-desethylsongorine, and deuterio analogs of songorine and of dihydrosongorine labeled in the hydroxyl groups and in the C_{12} methylene group.

An analysis of the mass-spectrometric data shows that molecules with the songorine skeleton differ markedly in their behavior under the action of electron impact from diterpene alkaloids with the lycoctonine skeleton [3]. Not only is the molecular ion stable, but the fragmentation of the molecules takes place in several directions, and not in one main direction, as is the case with the lycoctonine skeleton. However, the detachment of the substituent from C_1 plays some part, as before, especially in the molecules of the products of acetylation. In addition to this, following the cleavage of the $C_{14}—C_{17}$ bond the $C_{12}—C_{13}$ and $C_{10}—C_{11}$ bonds may break, as a result of which ketene or an acetyl radical may be expelled with the formation of ions having m/e 315 and 314 (Scheme 1). The M — 15 ions (7–10%) apparently arise through the splitting off of a methyl radical from the N-ethyl group, since this peak has a low intensity in the spectrum of N-desethylsongorine.

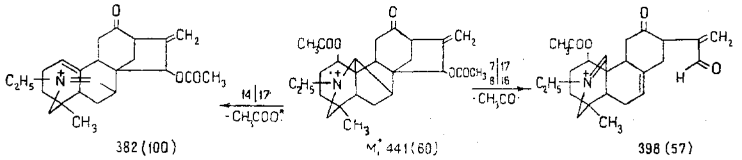
One of the most important rearrangement processes taking place when songorine and its derivatives are subjected to mass spectroscopy is the cleavage of ring A. The ions with m/e 298–300 probably appear after the initial cleavage of the $C_7—C_{17}$ bond. The strongest ion is that with m/e 298; however, it may also be formed by the expulsion of one of the hydroxyls from the ion-radical with m/e 315 after the cleavage of the $C_8—C_9$ bond. The fragment with m/e 300 is obtained in similar manner to the ion-radical with m/e 299, with subsequent migration of a hydrogen atom from C_2 to C_4.

Of great interest is the one-stage transition with the expulsion of the elements of rings C and D to form ions with 246 and 245 atomic mass units, which is confirmed by a metastable peak. The latter ion is apparently formed by the mechanism shown in Scheme 1 for the case of 246 m/e with the subsequent migration of a hydrogen atom from C_{13} to C_{10}. The group of small peaks with m/e 258–260 (3–4%) is evidently identical in origin with the group of ions mentioned, but it contains one carbon atom more (probably the C_{12} atom). This transition is also confirmed by a metastable peak. The ions with 298–300 amu, by losing the elements of rings C and D, and the ions with m/e 245 and 246, by splitting off a fragment of ring A, give rise by the above-mentioned mechanism to a group of ions with 186 and 188 amu. There is also a comparatively small peak of an ion with m/e 180, formed directly from the molecular ion (see Scheme 1). As a result of the loss of the lateral substituents by the ions with 186–188 and 180 amu a group of peaks of ions with m/e 147–152 appears. All the fragments containing ring C eliminate carbon monoxide or a formyl



Scheme 1. Fragmentation of songorine (relative intensities given in parentheses).

The mass spectrum of songorine diacetate is more meager than that of songorine. In addition to the M — 59 ion, analogous to the M — 17 ion in songorine, the diacetate is characterized by a high intensity of the M — 43 ion formed by the splitting off of an acetyl radical or an acetoxyl group from C$_{16}$.



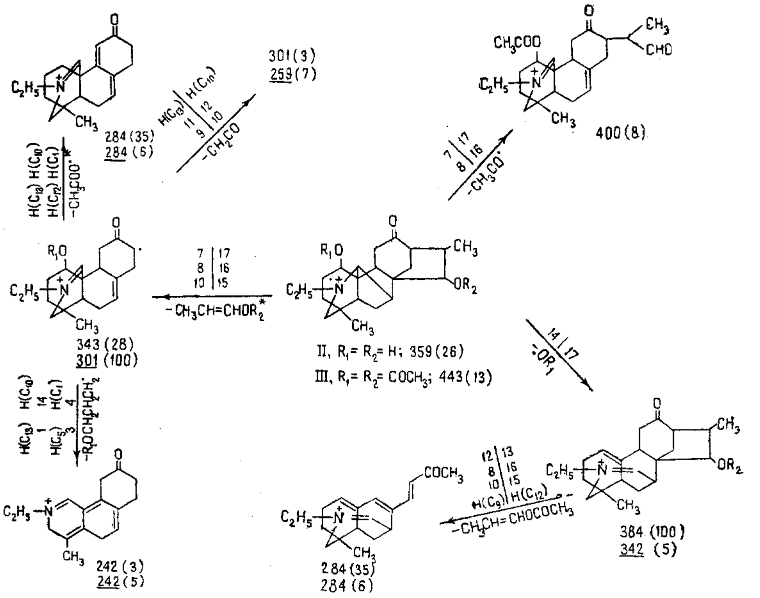
The ion with m/e 382 undergoes fragmentation to a small extent with the expulsion of CO or ketene by the mechanism shown in Scheme 1, and the ion with m/e 398 eliminates a molecule of acetic acid. There are no appreciable peaks in the region of lower mass numbers.

The main feature of the mass spectra of the hydrogenated derivatives is the presence of a strong M — 58 peak in the spectrum of dihydrosongorine (II) and the corresponding M — 100 peak in the spectrum of its diacetate (III). The appearance of these peaks is explained by the splitting out of the elements of ring D (Scheme 2). Subsequently, the ion-radical with m/e 301 (343) either expels ketene or cleaves ring A. In addition to the migration of the hydrogen atom shown in Scheme 2, in the expulsion of ketene the migration of hydrogen from C$_9$ to C$_{10}$ is possible, the subsequent expulsion of ketene being due to the cleavage of the C$_{10}$—C$_{11}$ and C$_{12}$—C$_{13}$ bonds.

The loss of ring A can also take place from the molecular ion-radical, which leads to an ion with m/e 300 in the case of dihydrosongorine and 342 in the case of its diacetate. The peak of the M—OR$_1$ ion, comparatively weak in hydrosongorine, becomes the maximum peak in the spectrum of its diacetate. According to the spectrum of the latter, in this case there are two processes, confirmed by metastable peaks, and leading to the formation of fragments with m/e 284 obviously having different structures (see Scheme 2). The splitting off of an acetyl radical from the molecular ion of hydrosongorine diacetate also takes place in analogy with what occurs in the fragmentation of songorine diacetate. Furthermore, an acetyl radical may also be expelled after the cleavage of the C$_{14}$—C$_{17}$ bond at the expense of ring C, as shown above. The ion with m/e 400 formed can apparently split out a formyl radical or acetic acid, giving fragments with m/e 370 and 340, respectively. As in the case of songorine, all the fragments containing ring C eliminate carbon monoxide.

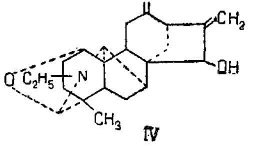
In the mass spectrum of songoramine, the peak of the M$^+$ ion has the maximum intensity. The intensity of the peak of the M — 17 ion present in the mass spectrum of songorine is low here.

Taking into account the difference in the compositions of songorine and songoramine (by two units) and the absence from songoramine of a hydroxyl group at C_1, it was natural to assume the presence of an oxygen bridge in its molecule. The ease of opening of the latter on hydrogenation permits the assumption that the bridge structure corresponds to an internal carbinol amine ether (IV). In this case, songoramine salts would be expected to have the structure V. In actual fact, in the IR spectrum of songoramine hydrochloride the absorption band at 2400–2700 cm^{-1} characteristic for NH is practically absent. The intensity of the band at 1665 cm^{-1} ($\nu_{C=\overset{+}{N}}$, $\nu_{C=C}$) has greatly increased, and in the region of the absorption of the hydroxyl groups two bands have appeared, at 3230 and 3400 cm^{-1}. For a definitive confirmation of the structure of songoramine, we carried out the transition from songorine to songoramine. When songorine was treated with silver oxide in aqueous alcoholic solution, two substances were obtained, one of which proved to be identical with songoramine; the second product was identified as N-desethylsongorine [3]. Thus, songoramine possesses the structure IV.

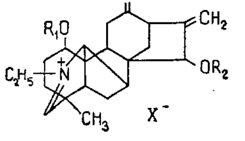


Scheme 2. Fragmentation of dihydrosongorine and its diacetate (the m/e values of the fragments formed from dihydrosongorine are underlined).

As mentioned above, on acetylation a substance was obtained which contained two acetyl groups. Its NMR spectra has two three-proton singlets at 2.05 and 2.09 ppm from the two acetyl groups. In its IR spectrum the intensities of not only the band at 1725 cm^{-1} but also of that at 1660 cm^{-1} have greatly increased, as was noted in the IR spectrum of songoramine hydrochloride. On the basis of these facts, the acetylation product must have the structure VI.



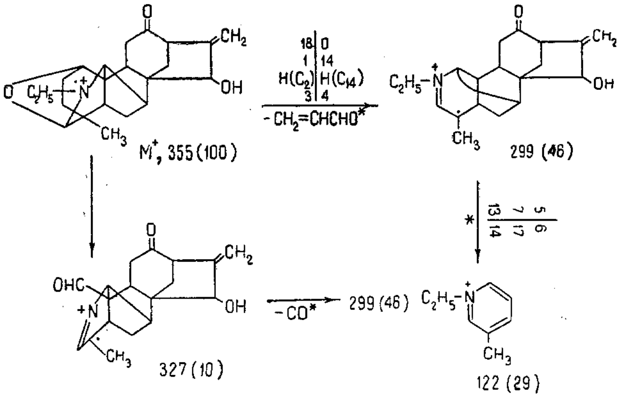
IV



V, $R_1=R_2=H$

VI, $R_1=R_2=COCH_3$.

So far as concerns the behavior of songoramine on mass spectrometry, the characteristic features of its fragmentation are connected with the presence of the carbinol amine internal ether grouping. The decomposition of the molecule begins with the cleavage of the oxygen bridge. The formation of the corresponding ion-radical initiates the splitting out of the elements of ring A in several directions, the main one of which leads to the expulsion of acrolein and the appearance of an ion-radical with m/e 299. The latter is converted in one stage into an ion with m/e 122. Both transitions are confirmed by metastable peaks. The peak of the ion with m/e 299 is composite; metastable peaks show that it is also formed through the successive splitting out of ethylene and carbon monoxide. A transition (confirmed by a metastable peak) corresponding to the splitting out of an acetyl radical from the ion with m/e 327 at the expense of ring C also takes place. In addition to this, an ion with 284 amu may be formed by the splitting out of a methyl radical from the ion-radical with m/e 299 (migration of the double bond to C_3—C_4 and detachment of a methyl radical from the N—CH_2CH_3 group). Of the ions connected with the far-reaching breakdown of the songoramine molecule the fragments with m/e 148 and 150 may be mentioned, these apparently having their origin from the ion with m/e 327 after the loss of the elements of rings B, C, and D. The spectrum of songoramine has, besides those mentioned, a strong peak of an ion with m/e 98. Its appearance is probably due to ionization at the keto group attached to C_{11}. The abundance of peaks of doubly-charged ions in all the spectra considered must be mentioned.



EXPERIMENTAL

The melting points are uncorrected. Chromatography was carried out on alumina (activity grade II). The NMR spectra were recorded on a JNM-4H-100/100 MHz instrument in deuterochloroform with HMDS as internal standard (values given in the δ scale), and the mass spectra on a MKh-1303 instrument with a system for the direct introduction of the substance into the ion source at 90–100° C at an ionizing voltage of 40 V.

Isolation of the alkaloids. 0.7 kg of comminuted air-dry roots of *A. karakolicum* was moistened with 5% ammonia solution and exhaustively extracted with chloroform. The combined chloroform extracts were treated with 5% H_2SO_4, the acid solution was washed with ether and made alkaline with ammonia. Extraction with ether then yielded 11.5 g of a mixture of alkaloids the treatment of which with acetone gave 2.3 g of aconitine. The mother solution, after evaporation and treatment with ether, yielded an additional 0.5 g of aconitine with mp 196–198° C (from acetone). The ethereal mother solution was evaporated, and the residue, after dissolution in ethanol and treatment with an ethanolic solution of HCl, formed 1.6 g of songorine hydrochloride with mp 240–244° C (decomp.). The ethanolic mother solution was diluted with water and an aqueous solution of sodium perchlorate was added. A noncrystalline product precipitated which was treated with methanol. This gave 1.8 g of songorine perchlorate with mp 236–238° C (decomp.; from ethanol). The aqueous ethanolic mother solution after the crystallization of the songorine perchlorate was made alkaline with ammonia, and the bases were extracted with ether. A solution of these bases in acetone was treated with nitric acid, giving 0.3 g of songorine nitrate with mp 225–227° (decomp.).

The aqueous mother solution after the isolation of the resinous perchlorate was made alkaline with ammonia and was shaken with ether. The residue after the distillation of the ether yielded songorine nitrate, and the mixture of bases (1.5 g) extracted from the mother solution was chromatographed on alumina (38 g). The bases were eluted with ether; the first fraction (50 ml) yielded 0.2 g of songoramine with mp 211–212° C (from acetone), and the second fraction, by treatment with acetone, yielded 0.3 g of songorine with mp 198–200° C. The third fraction [ether–chloroform (4 : 1)] gave 0.5 g of songorine and the fourth fraction [ether–chloroform (1 : 1)] 0.3 g of aconitine.

After recrystallization from a mixture of ether and methanol (1 : 1), the songoramine hydrochloride melted at 290° C.

Acetylation of songoramine. A solution of 0.27 g of the base in a mixture of 5 ml of acetic anhydride and 0.5 ml of pyridine was left at room temperature for 15 hr. The solution was evaporated and the residue was treated with water and, with ice cooling, it was made alkaline with sodium carbonate. The reaction product was extracted with chloroform. The crystalline product obtained after the distillation of the solvent melted at 110–115° C (from acetone).

Tetrahydrosongoramine. This was obtained by the hydrogenation of the base in ethanol over a platinum catalyst, mp 193–195° C (from acetone).

Oxidation of songorine with silver oxide. A mixture of 0.5 g of the base and the silver oxide obtained from 1.5 g of silver nitrate with 40 ml of 50% aqueous ethanol was stirred at room temperature for 3 days. The reaction mixture was filtered, evaporated to 20 ml, acidified with 10% H_2SO_4, and washed with chloroform. The aqueous solution was made alkaline with sodium carbonate and was shaken with chloroform. The first three portions of chloroform (150 ml), after the elimination of the solvent and treatment with acetone, gave 0.3 g of songoramine with mp 211–212° C (from acetone). The subsequent chloroform extracts (500 ml) were evaporated to dryness and the crystalline residue was washed with acetone. This gave 0.03 g of N-desethylsongorine identical in all respects with an authentic sample.

CONCLUSIONS

Aconitine, songorine, and songoramine have been isolated from Aconitum karakolicum. The structure of songoramine has been established on the basis of chemical and spectral characteristics. A scheme for the fragmentation of songorine and its derivatives has been proposed.

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