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STRUCTURE OF KORSEVERIDINE

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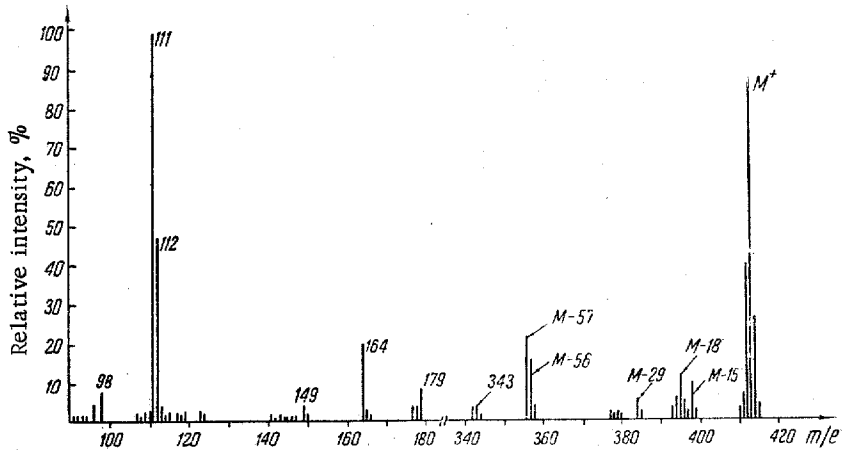
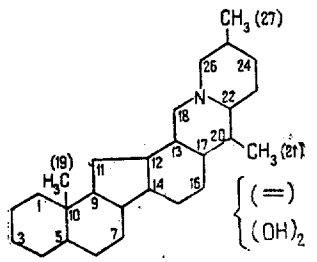
Korseveridine [1] has the composition $C_{27}H_{43}O_2N$, with both oxygen atoms in the form of hydroxy groups, and it forms a diacetyl derivative. Consequently, there are no tertiary hydroxy groups in this alkaloid. When diacetylkorseveridine is saponified in alcoholic alkali, the initial base is recovered. The IR spectrum of the diacetyl derivative has no absorption bands of hydroxy groups. Korseveridine and its diacetyl derivative in 1% sulfuric acid solution instantaneously decolorize a solution of potassium permanganate, which shows that they are unsaturated. Under the conditions for oxidizing secondary amino alcohols with chromic acid, the alkaloid undergoes a far-reaching change with the formation of a mixture of substances from which it was impossible to isolate a ketone. This property also shows the unsaturated nature of korseveridine. The double bond in korseveridine, as in the conversion products of jervine, is not hydrogenated in 10% acetic acid in the presence of platimum black [2]. The Oppenauer oxidation of korseveridine forms a monoketone—korseveridinone, the IR spectrum of which has absorption bands of a ketonic carbonyl and a hydroxy group. Consequently, in korseveridine both hydroxy groups are secondary.

Three C-methyl groups were determined in korseveridine by Kuhn-Roth oxidation, and this is confirmed by the presence in the NMR spectra of diacetylkorseveridine and of korseveridinone of signals from chemically equivalent methyl protons.



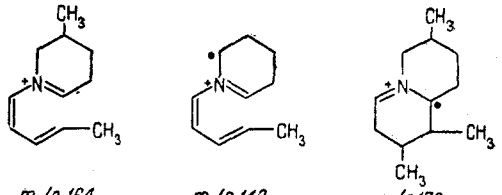
In the NMR spectrum of diacetylkorseveridine there is a singlet at 9.939τ (3H; C-19 CH_3), a doublet at 9.24τ (3H, C-21 CH_3), a doublet at 9.19τ (3H, C-27 CH_3) (J = 5 Hz), a singlet at 8.04τ (3H, $OCOCH_3$), a singlet at 8τ (3H, $OCOCH_3$), a multiplet at 4.98τ (H, $HCOCOCH_3$), and a multiplet at 5.5τ (H, $HCOCOCH_3$). The NMR spectrum of korseveridinone has a singlet at 9.24τ (3H, C-19 CH_3), a doublet at 9.22τ (3H, C-21 CH_3), and a doublet at 9.17τ (3H, C-27 CH_3) [2-5]. As can be seen from the data given, the presence in korseveridine of two secondary and one tertiary methyl groups shows that it is one of the C-nor-D-homosteroid alkaloids. In agreement with this, the mass spectrum of korseveridine (Figure) exhibits characteristic peaks of ions with m/e 98, 111, 112, 149, 164, 179, 356 $(M-57)^+$, 357 $(M-56)^+$, 395 $(M-18)^+$, 398 $(M-15)^+$, 413 (M^+). It is known that in the mass spectra of the C-nor-D-homosteroid alkaloids imperialine [6], zygacine [7], and verticine [8], the maximum peak is that of the ion with m/e 112. In the mass spectrum of korseveridine, the maximum peak is that of the ion with m/e 111, and the peak of the ion with m/e 112 has an intensity only 50% of that of the ion of maximum intensity. In the formation of the ion with m/e 112, a hydrogen ion in the base migrates from a hydroxy group on C_{20} and not from C_{17}, as has been shown in a study of the mass spectrum of zygacine [7]. Consequently, korseveridine, having no hydroxy group at C_{20}, forms the ion with m/e 111 with maximum intensity. On the basis of the data given above, the following structure is proposed for korseveridine:



The double bond in korseveridine may be located between C_8 and C_9, C_8 and C_{14}, C_{12} and C_{13}, C_{13} and C_{17}, C_{12} and C_{14}, C_{17} and C_{20}, or C_{20} and C_{22}. The remaining positions are excluded because of the absence in the NMR spectra of korseveridinone and of diacetylkorseveridine of a signal of an olefinic proton. The double bond cannot be between C_{17} and C_{20} or between C_{20} and C_{22}, either, since the NMR spectrum has no signal from the protons of a methyl group attached to a double bond. The fragments found with m/e 98, 111, and 112 are formed in accordance with a published scheme [6, 7]. In a study of the mass spectra of imperialine and its conversion products, we established a fragmentation scheme for C-nor-D-homosteroid alkaloids on the basis of which the ions with m/e 149, 164, and 179 must be formed from the heterocyclic rings D, E, and F.

As a result of α-, γ-, and β-cleavages, a hydrogen atom migrates from C_{18} to C_{16}, and an ion with m/e 164 is formed, the loss of a methyl group from the β position of which leads to the appearance of a fragment with m/e 149.

Cleavages of the bonds between C_{12} and C_{13} and between C_{15} and C_{16} must lead to the formation of an ion with m/e 179. In this, hydrogen ions migrate from C_{18} to C_{13} and from C_{22} to C_{16}.

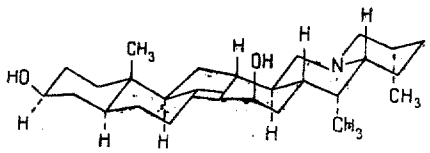


If the molecular ion of korseveridine has the double bond between C_{12} and C_{13}, C_{13} and C_{17}, C_{17} and C_{20}, or C_{20} and C_{22}, an energetically unfavorable state for α-cleavages with respect to the nitrogen atom arises and fragments with m/e 111 and 112 cannot be formed. If the double bond is located between C_{12} and C_{14}, the possibility of the formation of fragments with m/e 164 and 179 is excluded. The double bond cannot be between C_8 and C_9, either, since in this case the NMR spectrum of diacetylkorseveridine would have a signal from the C-19 CH_3 at about 9τ. Such a resonance signal is lacking from the NMR spectrum of diacetylkorseveridine, and the signal from the C-19 CH_3 is located at 9.39τ. Thus, the double bond in korseveridine is between C_8 and C_{14}. As already mentioned, the singlet in the NMR spectrum of korseveridinone is found at 9.24τ, and in the spectrum of diacetylkorseveridine it is at 9.39τ. It can be seen from this that when a ketonic carbonyl group and a hydroxy group are introduced in the place of two acetyl groups the signal shifts by 15 Hz. Such descreening is possible only if the carbonyl group is present in position 1, 3, 7, or 11 [2, 9]. The carbonyl group cannot be in position 11, since the ketone was obtained by Oppenauer oxidation. Under these conditions, a hydroxy group in steroids at C_{11} is not oxidized. If the carbonyl group were present in position 7, korseveridinone should have the characteristic maximum for α,β-unsaturated ketones in the UV spectrum, which is not the case.

When there is a carbonyl group in position 1, the signal from the C-19 methyl protons is displaced to a relatively larger extent in the direction of weak fields than when it is in position 3. In korseveridinone, on the other hand, this chemical shift is strongly screened, i.e., the carbonyl group is located in position 3. Consequently, one hydroxy group in korseveridine must be in the same position. The second hydroxy group cannot be attached to one of the carbon atoms of rings A and B, since the signal from the C-19 CH_3 group should resonate at approximately 9–9.1τ if two acetyl groups were present on any carbon atoms of rings A and B, which is not the case.

On the basis of the data given and the formation of fragments with m/e 111, 112, 164, and 179 from the molecular ion of korseveridine, the second hydroxy group must be at C_{11} or C_{15}. The instability of the diketone under the conditions of the oxidation of korseveridine with chromic acid gives grounds for assuming that the second hydroxy group is located at C_{15}.

On the basis of literature information on the NMR spectra of steroid compounds, we may conclude that the singlets in the NMR spectrum of korseveridinone and of diacetylkorseveridine are shifted considerably in the direction of strong fields. This property shows that in korseveridine rings A and B have a trans linkage and, accordingly, the C-19 methyl group and the C-5 H are in the trans position to one another. On the other hand, the IR spectra of korseveridine, diacetylkorseveridine, and korseveridinone have strong absorption bands of a trans-quinolizidine, showing the trans linkage of rings E and F. The hydroxy group at C_3 is in the β position, which is confirmed by the presence in the NMR spectrum of diacetylkorseveridine of a signal at 5.50τ (1 H, 3α H). The hydroxy group at C_{15} also apparently has the β orientation and, accordingly, in the NMR spectrum of diacetylkorseveridine there is a multiplet at 4.98τ (1 H, 15α H). If a linear structural formula is assumed for korseveridine, its most probably configuration can be shown in the following way:



The methyl groups at C_{20} and C_{25} are probably in the α positions, since the signals from their protons are observed in a comparatively strong field.

The correctness of the scheme of fragmentation of korseveridine has been confirmed by a study of the mass spectrum of korseveridinone. The spectrum of this compound shows the peaks of ions with m/e 111, 112, 149, 164, and 179 the ratio of the intensities of which is the same as in the spectrum of korseveridine. These results show once more the correctness of the scheme of fragmentation that we have proposed for the C-nor-D-homosteroid alkaloids [6]. The main difference between the mass spectra of korseveridine and korseveridinone is the following. In korseveridine there are peaks of ions with m/e 357 $(M - 56)^+$ and 356 $(M - 57)^+$, and in korseveridinone those with m/e 355 $(M - 56)^+$ and 356 $(M - 55)^+$. The $(M - 56)^+$ fragments are formed by the cleavage of the $C_{25}-C_{26}$ and $C_{22}-C_{23}$ bonds. The $(M - 55)^+$ ion arises after the cleavage of the C_3-C_4 bond, the migration of hydrogen from C_2 to C_4, and subsequent cleavage of the bond between C_1 and C_{10}. A similar scheme of bond cleavage for korseveridine gives the ion $(M - 57)^+$. The formation of the latter two fragments once again confirms position 3 for the carbonyl group of korseveridinone and establishes the position of a hydroxy group in korseveridine at C_3. The mass spectra of korseveridine and korseveridinone have the peaks of the ions $(M - 29)^+$, $(M - 18)^+$, and $(M - 15)^+$. The $(M - 29)^+$ fragment is formed mainly by the cleavage of the $C_{22}-C_{23}$ bond, the migration of the hydrogen from C_{26} to C_{23} and subsequent cleavage of the $C_{24}-C_{25}$ bond. The $(M - 18)^+$ ion appears through the splitting off of one of the hydroxy groups and hydrogen, and the $(M - 15)^+$ ion through the elimination of one of the methyl groups.

Experimental

The epigeal part of Korolkowii Sewerzowii Reg. collected at Saragach near Tashkent yielded 3.7% of total alkaloids in the early stage of development, 2.4% in the period before the flowering of the buds, and 1% in the flowering stage. The total alkaloids were isolated by ordinary chloroform extraction. The separation of the combined material according to solubilities yielded the alkaloid korseveridine with mp 290–292°C (from methanol), $[\alpha]_D$ -49.3° (c 0.852; 10% acetic acid). IR spectrum: ν_{max} 3310–3370 (OH), 2820–2960, 1430–1470 (C-CH_3), and 2745 cm^{-1} (trans-quinolizidine).

Found, % C 78.40; 78.50; H 10.7; 10;7; N 3.36; 3.35; mol. wt. 413 (from the mass spectrum). Calculated $C_{27}H_{43}O_2N$, %: C 78.39; H 10.47; N 3.38; mol. wt. 413, 62.

The hydrochloride was formed by treating the base with an alcoholic solution of hydrochloric acid. Mp 325–326°C (from methanol).

The hydrobromide was obtained by mixing an ethanolic solution of the base with 66% hydrobromic acid. Mp 314–315°C (from methanol).

The hydriodide was obtained in ethanolic solution by the action of 57% hydriodic acid. Mp 304–306° C (from methanol).

The methiodide. A methanolic solution of the base was boiled with methyl iodide for 2 hr to give the methiodide with mp 310–312°C (from methanol).

Diacetylkorseveridine. A mixture of 0.45 g of korseveridine, 7 ml of pyridine, and 3 ml of acetic anhydride was left at room temperature until dissolution was complete. Then the solution was evaporated in vacuum at 40° C. The residue was dissolved in chloroform and treated with 10% sodium carbonate solution. Then the chloroform layer was repeatedly washed with water. The residue from the distillation of the chloroform yielded crystals from acetone with mp 200–201° C. IR spectrum: ν_{max} 1735 cm^{-1}, 1250 cm^{-1} ($OCOCH_3$), 2870–2930, 1450–1470 cm^{-1} (C–CH_3), 2760 cm^{-1} (trans-quinolizidine). Singlet at 8τ (3 H, $OCOCH_3$), singlet at 8.04τ (3H, $OCOCH_3$).

Found, %: C 74.66; 74.47; H 9.65; 9.48. Calculated for $C_{31}H_{47}O_4N$, %: C 74.8; N 9.52.

Korseveridinone. To the aluminum phenoxide obtained from 200 mg of metallic aluminum and 150 ml of phenol in the presence of a crystal of iodine and mercury chloride was added 60 ml of benzene, 30 ml of acetone, and 200 mg of korseveridine, and the mixture was heated in the water bath for 4 hr. Then 100 ml of 5% caustic soda was added and the mixture was extracted with chloroform. The chloroform solution was washed with water and extracted with 5% sulfuric acid. The acid solution was washed with ether and was made alkaline, and the base was extracted with chloroform. The residue after the distillation of chloroform gave the initial korseveridine on treatment with acetone, while the

mother liquor after the addition of water yielded needle-like crystals with mp 123-124° C. IR spectrum: ν_{max} 3420 (OH), 1712 (C=O), 2820-2950, 1440-1470 (C-CH_3), and 2740-2765 cm^{-1} (trans-quinolizidine).

The IR spectra were taken on a UR-10 spectrophotometer in the form of moulded tablets with KBr and the mass spectra on a MKh-1303 instrument with a glass inlet system at 60 eV, 50 ma, and the NMR spectra in deuterochloroform on a JNM-4-H-100 instrument. Hexamethyldisiloxane was used as the internal standard.

Summary

The configuration 3β,15β-dihydroxy-5α,9α,13α,12β,17β,22β-$\Delta^{8(14)}$-cevine has been proposed for korseveridine.

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