STRUCTURE AND CONFIGURATION OF KORSEVERAMINE

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Korseveramine $C_{27}H_{45}O_3N$, is a saturated tertiary base isolated from Korolkowia sewerzowii Rgl. [1]; it forms a series of crystalline salts and derivatives.

The IR spectrum of the alkaloid has characteristic absorption frequencies at (cm^{-1}) 3610, 3430, 1053, and 1000 (hydroxy groups), 2960-2885 and 1460-1440 (C-methyl groups), and 2780 (trans-quinolizidine (Fig. 1).

The three oxygen atoms in korseveramine are present in the form of hydroxy groups, two of which acetylate with acetic anhydride in pyridine giving diacetylkorseveramine.

The IR spectrum of the diacetyl derivative shows absorption bands at (cm^{-1}) 3400 and 1040 (hydroxy groups), 2960-2870, 2810, 1460, and 1440 (C-methyl groups), 1735, 1725, and 1260-1250 (acetyl carbonyl groups), and 2770-2760 (trans-quinolizidine).

The absorption of a hydroxy group and two acetyl groups found in the IR spectrum permits the assumption that korseveramine contains one tertiary and two secondary hydroxy groups. Correspondingly, in the NMR spectrum of diacetylkorseveramine there are singlets from the chemically equivalent protons of two acetyl methyl groups at 1.97 and 2.02 ppm, and two one-proton signals at 5.03 and 4.57 ppm from hydrogens attached to carbons bearing acetyl groups, which definitively prove the secondary nature of the corresponding two hydroxy groups [2]. The absence from the spectrum of the diacetyl derivative of a signal between 3 and 4 ppm from a proton attached to a carbon with a hydroxy group and the above-mentioned resistance of one hydroxy group to acetylation unambiguously show the tertiary nature of the third hydroxy group of korseveramine. When korseveramine was oxidized with chromium trioxide in acetic acid, a diketone – korseveraminedione – was obtained (the two secondary hydroxy groups having been converted into carbonyl groups). Mol. wt. 427 (mass spectrum).

The IR spectrum of the ketone has absorption frequencies at (cm^{-1}) 3520-3410 and 1130 (hydroxy groups), 2960-2870, 1470, and 1430 (C-methyl groups), and 1710 (carbonyl groups).

Korseveramine and korseveraminedione undergo fragmentations under the conditions of mass spectrometry, forming similar characteristic fragments. The spectra of these substances differ by the values of the mass numbers of the molecular ions and the ions arising from them as the result of the ejection of fragments.

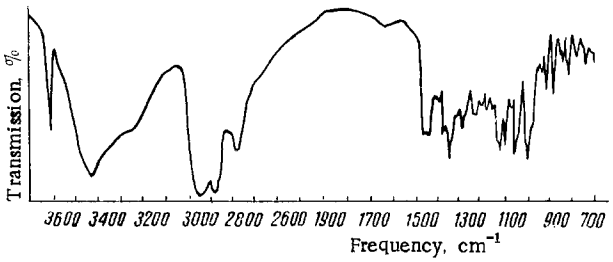

Fig. 1. IR spectrum of korseveramine.

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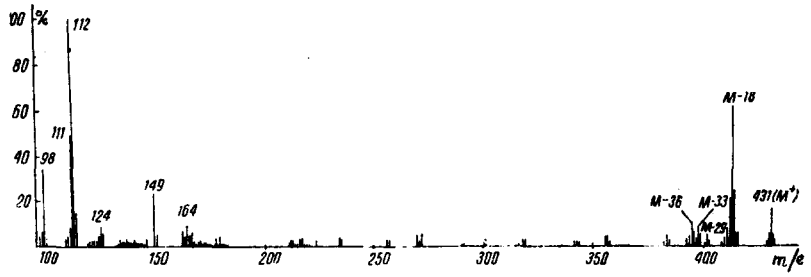


Fig. 2. Mass spectrum of korseveramine.

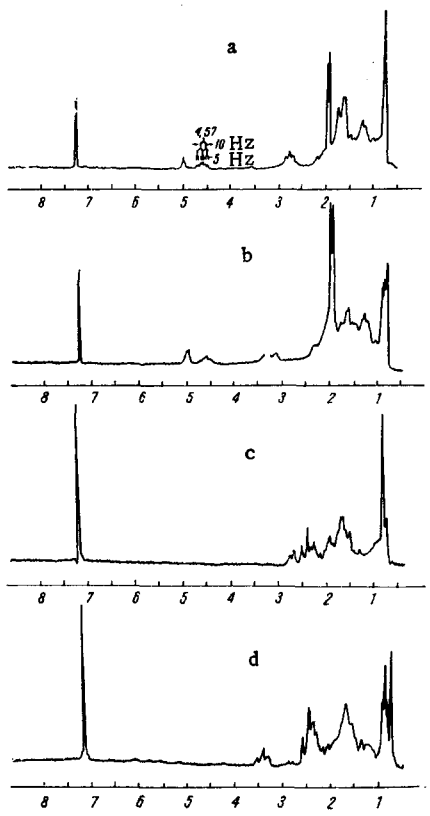


Fig. 3. NMR spectra of diacetylkorseveramine (taken in deuterochloroform) (a), diacetylkorseveramine (taken in deuterochloroform containing trifluoroacetic acid) (b), korseveraminedione (taken in deuterochloroform) (c), and korseveraminedione (taken in deuterochloroform containing trifluoroacetic acid) (d).

The mass spectrum of korseveramine has the peaks of ions with m/e 98, 111, 112, 124, 125, 149, 150, 162, 164, $(M-36)^+$; $(M-33)^+$; $(M-18)^+$; $(M-15)^+$; 431 (M^+), which are characteristic for the C-nor-D-homosteroid alkaloids of the cevine group [3, 4] (Fig. 2). The cevane skeleton of korseveramine is confirmed by the fact that its molecule contains 27 carbon atoms and the IR spectrum of the alkaloid and its derivatives clearly show the absorption of a trans-quinolizidine system. And, finally, its relationship to cevine was established from the characteristic values of the three three-proton signals from the chemically equivalent protons of the 19-CH_3, 21-CH_3, and 27-CH_3 groups observed in the NMR spectra of korseveramine derivatives [5-11].

The NMR spectrum of korseveramine was not recorded because of the poor solubility of the substance in deuterochloroform, pyridine, and benzene. The NMR spectrum of diacetylkorseveramine has singlets at (ppm) 0.79 (9H, 19-CH_3, 21-CH_3, and 27-CH_3), 1.97 (3H, $OCOCH_3$), and 2.01 (3H, $OCOCH_3$), a triplet at 2.77 (2H, $H_e-\overset{|}{C}-\overset{|}{N}-\overset{|}{C}-H_e$), a one-proton signal split into six lines at 4.57 (H, $H_a-COCOCH_3$), and a multiplet at 5.03 (H, $H_e-COCOCH_3$).

As can be seen from the spectrum of diacetylkorseveramine, the signals from the chemically equivalent protons of the 19-CH_3, 21-CH_3, and 27-CH_3 groups are superposed upon one another and appear in the form of a singlet. To investigate them individually, two drops of trifluoroacetic acid were added to a deuterochloroform solution of diacetylkorseveramine. A solution of the corresponding salt of the base was formed, and the nature of the spectrum changed. The NMR spectrum of diacetylkorseveramine in deuterochloroform in the presence of trifluoracetic acid exhibited singlets at (ppm) 0.79 (3H, 19-CH_3), 1.97 (3H, $OCOCH_3$), and 2.01 (3H, $OCOCH_3$), doublets at 0.86 (3H, 21-CH_3) and 0.86 (3H, 27-CH_3), and multiplets at 5.03 (H, $H_e-COCOCH_3$), 4.57 (H, $H_a-COCOCH_3$), and 3.25 (2H, $H_e-\overset{|}{C}-\overset{|}{N}-\overset{|}{C}-H_e$).

The results of a comparison of the NMR spectra of diacetylkorseveramine in deuterochloroform and in deuterochloroform containing trifluoroacetic acid show that the signals from the 21-CH_3 and 27-CH_3 groups and the two-proton multiplet of equatorial protons at carbon atoms connected with the nitrogen atom are superposed. The other characteristic signals in the absorption spectra do not change their positions; i.e., the values of the chemical shifts (CSs) in the two spectra are identical. Consequently, trifluoroacetic acid at the nitrogen atom of diacetylkorseveramine exerts its influence on the 21-CH_3 and 27-CH_3 groups

and also on the methylene protons connected to the nitrogen atom [11]. The other changes in the spectrum caused by changes in hydrogen bonds take place in the methylene region and are therefore difficult to describe.

The NMR spectrum of korseveraminedione has a singlet at (ppm) 0.86 (3H, 19-CH_3), doublets at 0.8 (3H, 27-CH_3), and an uncharacteristically split signal at 2.75 ppm (2H, $H_e C-N-CH_e$). In the spectrum of korseveraminedione, just as in the spectrum of diacetylkorseveramine, the lines of the 19-CH_3, 21-CH_3, and 27-CH_3 signals are superposed on one another. However, in the spectrum of korseveraminedione, because of the splitting of the lines of the signal, it is possible to observe doublets if values of 6 or 7 Hz are taken for the spin–spin splitting constants of the 21-CH_3 and 27-CH_3 secondary methyl groups, these figures having been established in many cases where there is a well-defined doublet from a secondary methyl group [7, 12, 13].

In the NMR spectrum of korseveraminedione taken in deuterochloroform containing trifluoroacetic acid there are well-defined doublets from the 21-CH_3 and 27-CH_3 groups: singlets at (ppm) 0.8 (3H, 19-CH_3), and doublets at 0.88 (3H, 21-CH_3), 0.94 (3H, 27-CH_3), and 3.45 (2H, $H_e-C-N-C-H_e$) (Fig. 3). Thus, it has been shown that in korseveramine there are two secondary and one tertiary methyl groups.

The facts given show that in the NMR spectra of diacetylkorseveramine and korseveraminedione the 21-CH_3 and 27-CH_3 protons have similar chemical shifts; they are not subject to the effects of the acetyl and carbonyl groups, while the chemical shift from 19-CH_3 group changes considerably with a change in the substituents. This shows that the secondary hydroxy groups in korseveramine are close to the 19-CH_3 group and very remote from the 21-CH_3 and 27-CH_3 groups.

Thus, in korseveramine the secondary hydroxy groups can be located only on the carbon atoms of rings A, B, and C, since in other positions acetyl and carbonyl groups scarcely change the chemical shift of a 19-CH_3 group [9, 14]. The IR spectrum of korseveraminedione shows the absorption band of a carbonyl group which is characteristic for two isolated carbonyl groups located in six-membered rings. Consequently, the assumption of the presence of a carbonyl group in position 11 in the five-membered ring C must be rejected.

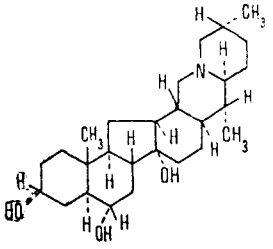
In the NMR spectra of diacetylkorseveramine and diacetylisodihydroimperialine, the 19-CH_3 signals appear at 0.79 ppm, and in the NMR spectra of korseveraminedione and imperialone the chemical shifts of the 19-CH_3 groups are 0.86 and 0.87 ppm, respectively [9]. On the basis of the identity of the values of the chemical shifts in the compounds compared, it has been shown that the hydroxy groups in korseveramine, as in isodihydroimperialine, are located at C_3 and C_6. However, the NMR spectrum of diacetylisodihydroimperialine, unlike that of diacetylkorseveramine, has the signals of two axial protons attached to carbons bearing acetyl groups [2]. As mentioned previously, the NMR spectrum of diacetylkorseveramine contains the signals from one axial proton and one equatorial proton attached to carbons bearing acetyl groups. According to these signals, the secondary hydroxy groups in korseveramine must be oriented similarly to the hydroxy groups in dihydroimperialine. With such an orientation, in diacetylkorseveramine the signal from the 19-CH_3 group should be found in the weaker field at 0.92 ppm, which is not the case. Consequently, in korseveramine the A/B and B/C rings are trans-linked and the hydroxy group at C_3 has the α-axial and that at C_6 the α-equatorial orientation. The configuration of the hydroxy group at C_6 is also confirmed by a one-proton signal split into six lines in the NMR spectrum of diacetylkorseveramine. Such splitting of the signal of the axial proton at C_6 takes place in the interaction of the axial protons at C_5 and C_7 and the equatorial proton at C_7 [1].

Under the conditions of mass spectrometry, korseveramine and korseveraminedione undergo fragmentation like alkaloids of the cevine group having no hydroxy substituent at C_{12}, C_{13}, C_{17}, C_{20}, C_{22}, or C_{26} [3]. Furthermore, according to the NMR spectra, the tertiary hydroxy group does not affect the chemical shifts of the 19-CH_3, 21-CH_3, and 27-CH_3 groups. The tertiary OH group must be located at C_{14} and have the α orientation.

The chemical shifts of the 19-CH_3, 21-CH_3, and 27-CH_3 groups in the NMR spectra of diacetylkorseveramine and korseveraminedione and the presence in the IR spectra of korseveramine and its derivatives

of the absorption bands of a trans-linked quinolizidine group show that the linkage of the rings in them is the same as in imperialine [3]. According to their chemical shifts, the 21-CH_3 and 27-CH_3 groups in korseveramine have the α-equatorial orientation.

Thus, on the basis of the facts given above, the structure and configuration of 5α,8β,9α,12α,13β,17α, 20β,22α,25β-cevane-3α,6α,14α-triol have been established for korseveramine.



Under the conditions of mass spectrometry, korseveramine and korseveraminedione form fragments according to the scheme described for korseverinine [1].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer (tablets with KBr), the mass spectra on an MKh-1303 instrument, and the NMR spectra on a JNM-4H-100 instrument in deuterochloroform with TMDS as internal standard.

Korseveramine. The substance was isolated from the ethereal fraction of the combined alkaloids of the epigeal part of Korolkowia sewerzowii. It precipitated from concentrated ethereal and acetonic solutions together with korseverinine and korseveridine [1, 15]. Korseveramine was isolated in the pure state by fractional recrystallization of the mixture of crystals from methanol. This base is sparingly soluble in petroleum ether, ether, benzene, chloroform, and pyridine and is soluble on heating in methanol and ethanol.

Korseveramine, $C_{27}H_{45}O_3N$, has mp 304-305°C (from methanol), $[\alpha]_D$ −14.63° (c 0.823; 10% acetic acid).

The hydrochloride was obtained by mixing ethanolic solutions of korseveramine and hydrogen chloride. mp 320-322°C (from methanol−acetone).

The hydrobromide was formed by treating korseveramine in ethanol with 57% hydrogen bromide. mp 316-318°C (from acetone).

Diacetylkorseveramine. A mixture of 20 mg of korseveramine in 1 ml of acetic anhydride and 2 ml of pyridine was left at room temperature. The resulting solution was evaporated in vacuum, and the residue was treated with water and made alkaline with a saturated solution of sodium bicarbonate. The reaction product was extracted from the alkaline solution with chloroform. The solvent was distilled off, the pyridine was eliminated in vacuum, and the residue was purified by recrystallization from petroleum ether. The melting point of diacetylkorseveramine was 174-175°C (from petroleum ether), R_f 0.6 on Al_2O_3 and $CaSO_4$ (9 : 1) in the ethyl acetate−chloroform−methanol (30 : 20 : 3) system.

Korseveraminedione. A mixture of 100 mg of korseveramine, 50 mg of chromium trioxide, and 3 ml of acetic acid was heated in the boiling water bath for 20 min. Then the solution was diluted with water and made alkaline with a saturated solution of sodium bicarbonate, and the base was extracted with chloroform. The residue after the elimination of the solvent was dried in vacuum, dissolved in benzene, and chromatographed on alumina. Benzene eluates, after concentration and standing, deposited crystals with mp 215-217°C (from benzene), R_f 0.14 on Al_2O_3 and $CaSO_4$ (9 : 1) in the petroleum ether−toluene−methanol (5 : 5 : 0.5) system. Mol. wt. 427 (mass spectrum).

CONCLUSIONS

A new alkaloid has been isolated, and its structure and configuration have been established as 5α,8β, 9α,12α,13β,17α,20β,22α,25β-cevane-3α,6α,14α-triol.

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