# Study of alkaloids from the flora of the Siberian and Altai regions. 6.* Crystal and molecular structure of songorine *Z*-oxime

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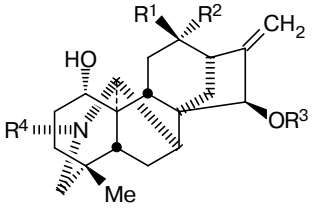
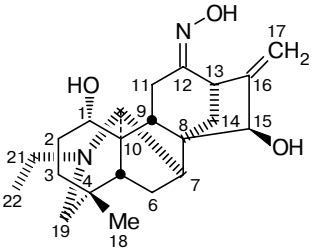
Oximation of songorine afforded a mixture of its *Z*- and *E*-oximes. The crystal and molecular structure of the *Z*-isomer was established by X-ray diffraction analysis. Its structure was also confirmed by the spectral data (2D $^1$H—$^1$H and $^{13}$C—$^1$H NMR spectroscopy and mass spectrometry). The structure of isomeric *E*-oxime was established by comparing its NMR spectroscopic data ($^1$H and $^{13}$C) with the data for the *Z*-isomer.

**Key words:** diterpene alkaloids, songorine, oxime, X-ray diffraction analysis, 2D NMR spectroscopy.

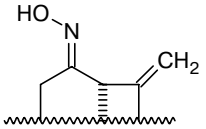
To our knowledge, data on carbonyl-substituted derivatives of the diterpene alkaloid songorine (**1**), such as *Z*- and *E*-oximes, are lacking. Songorine (**1**) possessing the cycloveatchane skeleton was discovered in 1948.[2] Its absolute configuration was determined by comparing with the absolute configuration of lucidusculine hydroiodide (**2**), which has been unambiguously established by X-ray diffraction analysis.[3]



**1**, **2**, **4**



(*Z*)-**3**



(*E*)-**3**

| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **1** | O | O | H | Et |
| **2** | H | OH | Ac | Et |
| **4** | O | O | H | Me |

We obtained a mixture of isomeric songorine *Z*- and *E*-oximes ((*Z*)-**3** and (*E*)-**3**, respectively) in 77% yield by standard oximation. For these oximes, the molecular formula $C_{22}H_{32}N_2O_3$ was established based on the precise *m/z* value for the molecular ion $[M]^+$. According to the $^1$H and $^{13}$C NMR spectra (a 10% solution in $CD_3OD/CDCl_3$, 4 : 1 v/v), the ratio of the isomers (*Z* : *E*) was 1.67 : 1. Cooling of the above-mentioned solution to 0 °C afforded the crystal solvate of individual oxime (*Z*)-**3** of composition $C_{22}H_{32}N_2O_3 \cdot CDCl_3$, which was determined by X-ray diffraction study of its single crystal. The three-dimensional molecular structure of isomer (*Z*)-**3** is shown in Fig. 1. The bond lengths in the molecule are close to standard values.[4] The C(9)—C(10) bond (1.575(5) Å) is slightly elongated compared to the average value (1.556(11) Å[4]). The corresponding bond length in finetianine (**4**),[5] which is the closest analog of songorine (**1**), is 1.562 Å. The six-membered ring in **3** consisting of the C(1)—C(5) and C(10) atoms, like the analogous ring in finetianine (**4**), adopts a chair conformation flattened in the region of the C(1) and C(2) atoms. Interestingly, this ring in finetianine hydrobromide (**4**)[5] also adopts a chair conformation, whereas this ring in lucidusculine hydroiodide (**2**)[6] has a distorted boat conformation. In molecule **1**, the ring consisting of the C(8), C(9), and C(11)—C(14) atoms adopts a flattened boat conformation, which is also typical of finetianine (**4**), its hydrobromide, and lucidusculine hydroiodide (**2**). In the structure of (*Z*)-**3**, the following intermolecular hydrogen bonds and a shortened[7] van der Waals contact are observed: O(12)—H...O(1) (O—H, 0.72(4) Å; H...O, 1.97(5) Å; O—H...O, 167(5)°), O(15)—H...N(12) (O—H, 0.75(5) Å; H...N, 2.21(5) Å; O—H...N, 169(5)°), and C(1)S—D...O(12) (C—D 0.98 Å; D...O, 2.43 Å; C—D...O, 127°). The structure of isomer

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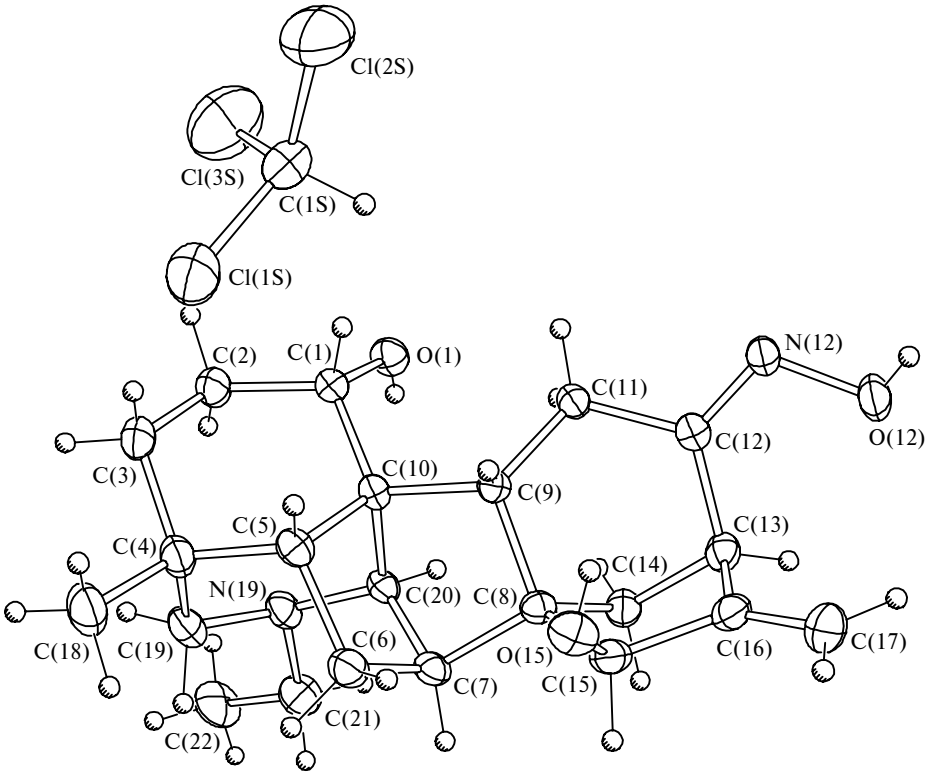


**Fig. 1.** Three-dimensional molecular structure of songorine oxime (*Z*)-**3** · $CDCl_3$.

(*Z*)-**3** was also confirmed by the spectral data ($^1H$ and $^{13}C$ NMR spectroscopy and mass spectrometry; see the Experimental section).

The structure of isomeric songorine oxime (*E*)-**3** was established by comparing its $^1H$ and $^{13}C$ NMR spectra with the spectra of isomer (*Z*)-**3**.

## Experimental

The IR spectra were recorded on a Vector 22 spectrometer. The molecular weights and elemental compositions were determined on a Finnigan MAT high-resolution mass spectrometer (model MS 8200) (EI, the energy of ionizing electrons was 70 eV). The melting point was determined on a Kofler stage. The optical rotation was measured on a Polamat A polarimeter (Carl Zeiss, Germany).

The $^1H$ and $^{13}C$ NMR spectra, the 2D $^1H$—$^1H$ (COSY) and $^{13}C$—$^1H$ NMR spectra (125 Hz for COSY and 7 Hz for COLOC), and the 2D-INADEQUATE NMR spectra were recorded on a Bruker DRX 500 instrument (500.13 MHz for $^1H$ and 125.76 MHz for $^{13}C$) with resonance stabilization based on the signal for deuterium of the solvent ($CDCl_3$) using the standard Bruker software. The chemical shifts were measured relative to the signals of $CDCl_3$ as the internal standard: $\delta_H$ 7.24 and $\delta_C$ 76.90. The multiplicities of the signals in the $^{13}C$ NMR spectrum were determined according to standard procedures in the *J*-modulation mode and using the off-resonance irradiation of protons.[8]

Freshly distilled solvents and the reagents of chemically pure grade were used. Songorine (**1**) was isolated from air-dried roots of wild monkshood (*Aconitum barbatum* Pers., the family *Ranunculaceae*), which were collected in the Altai region (in the neighborhood of Maima; July 1999), m.p. 201—203 °C (MeOH), $[\alpha]^{20}_{578}$ −148 (*c* 4.8, anhydrous EtOH). Lit. data[2]: m.p. 201—203 °C (MeOH), $[\alpha]_D$ −140 (*c* 1.27, anhydrous EtOH). $^1H$ NMR (a 10% solution in $CDCl_3$), δ: 0.67 (s, 3 H, $C(18)H_3$); 0.97 (t, 3 H, $NCH_2Me$, $J$ = 7.2 Hz); 1.22—1.30 (m, 3 H, $H_a(3)$, H(5), $H_a(6)$); 1.35 (dd, 1 H, $H_a(14)$, $J$ = 12.5 and 4.0 Hz); 1.51 (dt, 1 H, $H_b(3)$, $J$ = 13.5 and 4.5 Hz); 1.67 (dd, 1 H, H(9), $J$ = 11.0 and 7.0 Hz); 1.76—1.83 (m, 1 H, $H_a(2)$); 2.00 (d, 1 H, $H_b(14)$, $J$ = 12.5 Hz); 2.01—2.09 (m, 1 H, $H_b(2)$); 2.12—2.18 (m, 2 H, H(7), $H_a(19)$); 2.21 (dd, 1 H, $H_a(11)$, $J$ = 17.0 and 7.0 Hz); 2.31—2.52 (m, 5 H, $H_b(6)$, $H_b(19)$, $C(21)H_2$, C(1)OH); 2.87 (d, 1 H, C(15)OH, $J$ = 8.0 Hz); 2.97 (d, 1 H, H(13), $J$ = 3.5 Hz); 3.21 (dd, 1 H, $H_b(11)$, $J$ = 17.0 and 11.5 Hz); 3.35 (br.s, 1 H, H(20)); 3.74 (dd, 1 H, H(1), $J$ = 9.3 and 6.7 Hz); 4.24 (d, 1 H, H(15), $J$ = 8.0 Hz); 5.09 and 5.16 (both br.s, 1 H, $\Delta\nu_{1/2}$ = 6.0 Hz, $C(17)H_2$). The $^1H$ NMR spectral data for songorine published in the literature[9] differ from those reported above due to limitations of the NMR methods used in the cited study. The chemical shifts of the carbon atoms in the $^{13}C$ NMR spectrum of the same solution (125.76 MHz, δ) are virtually identical with those reported in the literature.[10] The assignment of the signals in the $^{13}C$ NMR spectrum of songorine (**1**) was made using the 2D-INADEQUATE procedure.[11] It was found that the assignments of the signals for the C(3) and C(14) atoms of songorine reported previously[10] must be interchanged.

The assignments of the signals in the $^{13}C$ NMR spectra of oximes (*Z*)-**3** and (*E*)-**3** were made by comparing their chemical shifts and multiplicities with the corresponding signals of songorine taking into account the anisotropic effect of the oxygen atom of the hydroxyimino group. This effect is manifested in the upfield shifts of the signals for the *syn*- and *anti*-carbon atoms (C(11) and C(13)) of oximes by ~13—14 and ~9 ppm, respectively, compared to the signals for these atoms in songorine (*cf.* lit. data[12—14]).

**X-ray diffraction study** of isomeric oxime (*Z*)-**3** was carried out on a Bruker P4 diffractometer (Mo-Kα radiation, graphite monochromator) using a single crystal of dimensions 0.25×0.35×0.60 mm. The intensities of 2314 independent reflections were measured in the scan range $2\theta < 50°$ using the θ/2θ-scanning technique. Corrections were applied for a decrease in the intensities of the check reflections (4.9%) and for absorption (transmission was 0.921—0.988) by the semiempirical method based on the data of ψ scanning. The structure was solved by the direct method using the Bruker-XS program and refined by the full-matrix least-squares method in the anisotropic-isotropic approximation using the SHELXL-97 program package to $wR_2 = 0.1378$, $S = 1.037$ for all reflections ($R = 0.0493$ based on 2028 reflections with $F_0 > 4\sigma$). The parameter of the absolute structure is 0.11(16), which corresponds to the expected zero value for the correct absolute structure.

The atomic coordinates and thermal parameters were deposited with the Cambridge Structural Database.

**A mixture of songorine *Z*- and *E*-oximes (*Z*- and *E*-21-ethyl-1,15-dihydroxy-12-hydroxyimino-4-methyl-16-methylene-7,20-cycloveatchanes) ((*Z*)-3 and (*E*)-3).** Water (2 mL) was added to a mixture of $NH_2OH \cdot HCl$ (0.38 g, 5.5 mmol) and anhydrous $K_2CO_3$ (0.38 g, 2.8 mmol). After cessation of $CO_2$ evolution, a solution of songorine (**1**) (0.42 g, 1.2 mmol) in MeOH (6.8 mL) was added and the reaction mixture was refluxed for 1 h. The solvent was removed *in vacuo* and the residue was extracted with $CHCl_3$ (3×20 mL). After removal of the solvent from the extract and drying of the residue at 100 °C (3 Torr), a crystalline mixture of *Z*- and *E*-oximes (*Z*/*E* = 1.67 : 1) was obtained in a yield of 0.33 g (77%).

Crystals of the solvate of individual **Z-oxime** were isolated from a 10% solution of this mixture in $CD_3OD/CDCl_3$ (4 : 1 v/v) upon cooling to 0 °C. The composition $C_{22}H_{32}N_2O_3 \cdot CDCl_3$ was established by X-ray diffraction analysis. The crystallographic data for the solvate: the orthorhombic system, $a = 6.8233(6)$, $b = 18.444(1)$, $c = 19.223(1)$ Å, $V = 2419.2(3)$ Å$^3$, space group $P2_12_12_1$, $C_{22}H_{32}N_2O_3+CDCl_3$, $M = 492.86$, $Z = 4$, $D_c = 1.353$ g cm$^{-3}$, $\mu = 0.406$ mm$^{-1}$. The solvate lost the solvent molecule upon heating (100 °C, 3 Torr). The resulting product had the m.p. of 210—212 °C, $[\alpha]^{20}_{578}$ +12.9 (*c* 3.1, MeOH). The high-resolution mass spectrum, *m*/*z*: 372.2407 $[M]^+$. $C_{22}H_{32}N_2O_3$. Calculated: *M* 372.2413. $^1$H NMR (a 10% solution in $CD_3OD/CDCl_3$, 4 : 1 v/v), δ: 0.79 (s, 3 H, C(18)$H_3$); 1.12 (t, 3 H, $NCH_2C\underline{H}_3$, $J = 7.2$ Hz); 1.21 (dd, 1 H, $H_a$(14), $J = 12.5$ and 4.0 Hz); 1.33—1.40 (m, 3 H, $H_a$(3), H(5), $H_a$(6)); 1.62 (dt, 1 H, $H_b$(3), $J = 13.5$ and 4.5 Hz); 1.80—1.86 (m, 1 H, $H_a$(2)); 1.90 (dd, 1 H, H(9), $J = 12.0$ and 7.0 Hz); 1.95 (d, 1 H, $H_b$(14), $J = 12.5$ Hz); 2.20 (d, 1 H, H(7), $J = 5.0$ Hz); 2.24 (dd, 1 H, $H_a$(11), $J = 16.0$ and 7.0 Hz); 2.30 (d, 1 H, $H_a$(19), $J = 12.0$ Hz); 2.30—2.39 (m, 1 H, $H_b$(2)); 2.49 (dq, 1 H, $H_a$(21), $J = 12.5$ and 7.2 Hz); 2.59 (d, 1 H, $H_b$(19), $J = 12.0$ Hz); 2.61* (m, 1 H, $H_b$(6)); 2.65 (dq, 1 H, $H_b$(21), $J = 12.5$ and 7.2); 3.05 (dd, 1 H, $H_b$(11), $J = 16.0$ and 12.5 Hz); 3.48 (br.s, 1 H, H(20)); 3.89—3.93 (m, 2 H, H(1), H(13)); 4.24 (t, 1 H, H(15), $J = 2.0$ Hz); 5.17 and 5.53 (both br.s, 1 H each, $\Delta\nu_{1/2} = 6.0$ Hz, C(17)$H_2$). The $^{13}$C NMR spectrum of the same solution, δ: 71.94 (C(1)), 32.54 (C(2)), 39.17 (C(3)), 35.38 (C(4)), 51.06 (C(5)), 24.02 (C(6)), 45.79 (C(7)), 51.01 (C(8)), 39.31 (C(9)), 53.50 (C(10)), 28.81 (C(11)), 162.29 (C(12)), 40.79 (C(13)), 32.15 (C(14)), 77.87 (C(15)), 154.90 (C(16)), 111.48 (C(17)), 26.59 (C(18)), 58.50 (C(19)), 67.06 (C(20)), 52.30 (C(21)), 13.72 (C(22)). IR (KBr), ν/cm$^{-1}$: 752, 881, 908, 927, 945, 1004, 1040, 1104, 1376, 1399, 1456, 1486, 1652 (C=N), 2827, 2871, 2929, 2970, and 3010.

The $^1$H NMR spectrum of the above-mentioned solution of the mixture of the *Z*- and *E*-isomers has individual signals for the protons of the ***E*-isomer**: 3.38 (br.s, 1 H, H(20)); 4.26 (t, 1 H, H(15), $J = 2.0$ Hz), 5.16 and 5.25 (both br.s, 1 H each, $\Delta\nu_{1/2} = 6.0$ Hz, C(17)$H_2$); the remaining signals overlap with the signals of the *Z*-isomer. The $^{13}$C NMR spectrum of the solution of this mixture has the following signals for the carbon atoms of the *E*-isomer: 71.08 (C(1)), 32.55 (C(2)), 38.39 (C(3)), 35.24 (C(4)), 50.55 (C(5)), 22.18 (C(6)), 45.10 (C(7)), 50.50 (C(8)), 38.10 (C(9)), 53.40 (C(10)), 23.61 (C(11)), 163.95 (C(12)), 44.16 (C(13)), 32.18 (C(14)), 77.53 (C(15)), 155.53 (C(16)), 110.70 (C(17)), 26.61 (C(18)), 58.38 (C(19)), 67.08 (C(20)), 52.35 (C(21)), 13.45 (C(22)).

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* The center of the multiplet overlapping with the signals of C(19)$H_2$ is given.

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