

THE STRUCTURE OF KORSINE

R. N. Nuriddinov, A. I. Saidkhodzhaev, and S. Yu. Yunusov

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A new crystalline alkaloid korsine has been isolated from the bulbs of *Korolkowia sewerzovii* Rgl. [1-4]. The base forms crystalline hydrochloride, hydrobromide, hydriodide, methiodide, and triacetyl derivatives. Korsine contains three C-methyl groups, a tertiary nitrogen atom, and three secondary hydroxy groups, and has no N-methyl group. The IR spectrum of the base has absorption bands of hydroxy and C-methyl groups, of a double bond, and of a trans-linked quinolizidine system.

The hydrogenation of korsine gives dihydrokorsine $C_{27}H_{45}O_3N$, the oxidation of which yields dihydrokorsinone $C_{27}H_{43}O_3N$.

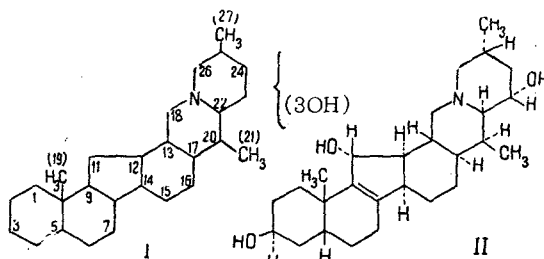
The IR spectrum of the ketone has absorption bands of hydroxy, C-methyl, and carbonyl groups and of a trans-quinolizidine system, and the UV spectrum has an absorption maximum at 290 m μ (Fig. 1), which is characteristic for the steroid alkaloids [5, 6]. The oxidation of korsine gives korsinone $C_{27}H_{41}O_3N$ and korsinedione $C_{27}H_{39}O_3N$, from which mono- and dioximes, respectively, have been obtained. The IR spectra of these ketones have the absorption bands of hydroxy, carbonyl, and C-methyl groups. The reduction of korsinone leads to the formation of dihydrokorsine, which shows the retention of the heterocyclic skeleton when the base is oxidized.

The UV spectrum of korsinone has λ_{max} 245 and 300 m μ , which are characteristic of α, β -unsaturated ketones.

Under the conditions of fragmentation mass spectrometry, the action of electronic impacts subjects korsine and korsinedione to fragmentation similar to that of the C-nor-D-homosteroid alkaloids [7, 8].

The mass spectrum of korsine has peaks of ions with m/e 114, 127, 128, 141, 155, 178, 180, 194, $(M - 71)^+$, $(M - 57)^+$, $(M - 45)^+$, $(M - 36)^+$, $(M - 29)^+$, $(M - 18)^+$, $(M - 15)^+$ and 429 $(M)^+$ (Fig. 2).

The presence of three C-methyl groups, the fact that the molecule contains 27 carbon atoms, the results of fragmentation under the conditions of the mass spectrometry of korsine, and the nature of the curve and the absorption maximum in the UV region of the spectrum of dihydrokorsinone permit the heterocyclic skeleton (I) to be put forward for korsine.



Formula (I) is confirmed by the mass and NMR spectra of korsine and the products of its transformation. The NMR spectrum of korsine* has doublets at 9.20 τ (3H, C-27 CH_3), 9.21 τ (3H, C-21 CH_3), and a singlet at 9.04 τ (3H, C-19 CH_3) (Fig. 3). The NMR spectrum of triacetylkorsine has the following resonance signals: doublet at 9.17 τ (3H, C-27 CH_3) and 9.17 τ (3H, C-21 CH_3), singlets at 8.81 τ (3H, C-19 CH_3), 8.06 τ (6H, 2 $COOCH_3$), and 8.02 τ (3H, $COOCH_3$), and multiplets with centers at 5.35 τ (1H; $HCOOCH_3$) and 5.06 τ (2H, 2 $HCOOCH_3$).

The NMR spectrum of triacetyldihydrokorsine has the following signals: doublets at 9.18 τ (3H, C-27 CH_3) and 9.22 τ (3H, C-21 CH_3), singlets at 9.04 τ (3H, C-19 CH_3), 8.04 τ (6H, 2 $COOCH_3$), and 8.00 τ (3H, $COOCH_3$) and multiplets with centers at 5.35 τ (1H, $HCOOCH_3$) and 5.08 τ (2H, 2 $HCOOCH_3$) (see Fig. 3). In the NMR spectrum of korsinone there are doublets at 9.17 τ (3H, C-27 CH_3) and 9.1 τ (3H, C-21 CH_3) and a singlet at 8.8 τ (3H, C-19 CH_3) (9-15).

* The spectrum of korsine was taken in $(D_3C)_2SO$ and therefore the features of this spectrum are not discussed here.

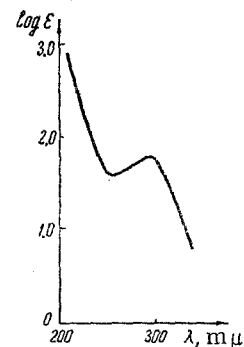


Fig. 1. UV spectrum of dihydrokorsinone (in ethanol).

The fragmentation of korsine and korsinedione take place similarly to the fragmentation of the alkaloids imperialine, zygacine, and edpetilidine [7,8]. In the mass spectra of the last three alkaloids, in the region of low mass

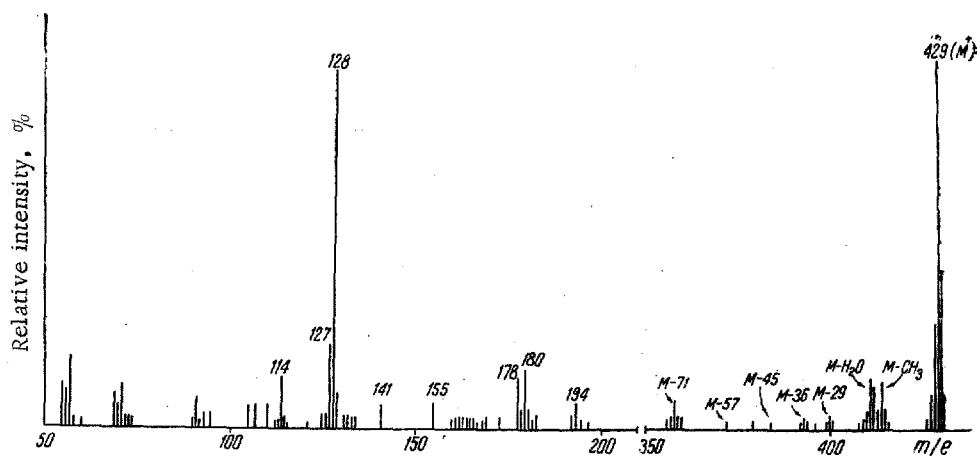


Fig. 2. Mass spectrum of korsine.

numbers there are peaks of ions with m/e 98, 111, and 112. In the spectrum of korsine there are peaks with m/e 114, 127, and 128, and in the spectrum of korsinedione peaks with m/e 112, 125, and 126. As can be seen, the fragments

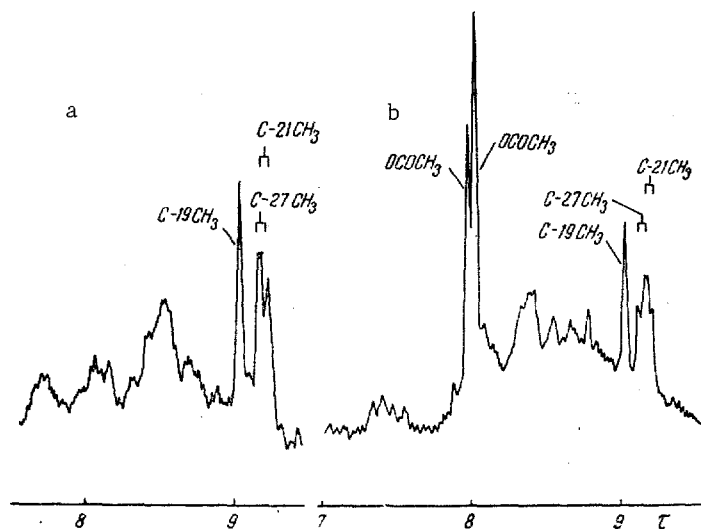


Fig. 3. NMR spectra of korsine (a) and triacetyldihydrokorsine (b).

of korsine differ from the corresponding ions of imperialine, zygacine, and edpetilidine by 16 mass units. This shows that one hydroxy group in korsine may be located in the heterocyclic skeleton of korsine at C_{18} , C_{23} , C_{24} , or C_{26} .

The mass numbers given for korsine and korsinedione differ by two units. Consequently, in the molecule of korsinedione one carbonyl group is also present in position 18, 23, 24, or 26. Thus, in the oxidation of korsine two secondary alcohol groups are oxidized to ketonic carbonyl groups and one of them is located at C_{18} , C_{23} , C_{24} , or C_{26} . If korsinedione had a carbonyl group in position 18 or 26, it would possess the properties of amides, and if korsine had a hydroxy group at C_{18} or C_{26} it would possess the properties of a carbinol amine. Finally, there is no absorption of an amide carbonyl group in the IR spectrum of korsinedione. Consequently, the location of a hydroxy group of korsine at position C_{18} or C_{26} is excluded.

The results of a discussion of the biogenesis of the steroid and the C-nor-D-homosteroid alkaloids makes it possible to assume a position at C_{23} for a hydroxy group. This is confirmed by the presence in the NMR spectra of triacetylkorsine, triacetyldihydrokorsine, and korsinone of resonance signals from chemically equivalent protons of 21- and 27-methyl groups (9.17–9.22 τ) corresponding to acetyl and hydroxy groups arranged symmetrically with respect to the nitrogen atom. Consequently, one hydroxy group is located at C_{23} .

The absence from the NMR spectrum of triacetylkorsine and korsinone of an olefinic proton permits the assumption of a position between C_8 and C_9 , C_8 and C_{14} , C_{12} and C_{13} , C_{12} and C_{14} , C_{13} and C_{17} , C_{17} and C_{20} , or C_{20}

and C₂₂ for the double bond. The latter two positions are excluded because of the absence from the NMR spectrum of a singlet from the protons of a methyl group attached to an unsaturated carbon atom.

If the double bond were present between C₁₃ and C₁₇, C₁₂ and C₁₃, or C₁₂ and C₁₄, fragments with m/e 178 and 180 could not be formed from korsine and fragments with m/e 176 and 178 from korsinedione under the conditions of mass spectrometry. If the double bond were located between C₈ and C₁₄, the resonance signals from the protons of the 19-methyl group of korsine should shift to a weaker field after hydrogenation of the double bond, i.e., deshielding should take place which, however, is not the case. In triacetyldihydrokorsine the signal from the protons of the 19-methyl group is shielded to a greater extent than in triacetylkorsine. These data exclude the location of the double bond between C₈ and C₁₄, and the only possible position remaining for it is between C₈ and C₉. Hence, the second hydroxy group must be located at C₇ or C₁₁, since the UV spectrum of korsine has an absorption maximum characteristic for α,β -unsaturated ketones.

The IR spectrum of korsine has absorption bands at 1090, 1056, and 1010 cm⁻¹ characteristic of hydroxy groups, of which the band at 1056 cm⁻¹ is characteristic for a β -OH group in Δ^5 steroids [16,17]. In steroid compounds, after the acetylation of a β -OH group an absorption band appears at 1030 cm⁻¹. Likewise, in triacetylkorsine there is an absorption band at 1028 cm⁻¹. Thus, korsine contains a β -OH group and a hydrogen atom at C₅ oriented in the β position.

Furthermore, in the NMR spectrum of triacetyldihydrokorsine the resonance signal from the protons of the 9-methyl group is found at 9.04 τ , while the electron density of the 19-methyl group is explained by the influence of two acetyl groups. If we take into account the deshielding influence of these groups, it is possible to show approximately that in the oxygen-free compound korsine the signal from the 19-methyl group will be located at 9.16 τ . This value is very close to the chemical shift found for the 19-methyl group in the Δ^5 -C-nor-D-homosteroids. This once again confirms that the hydrogen atom at C₅ in korsine has the β orientation. It has been observed that the signals from the 19-methyl group of korsinone and triacetylkorsine is located at 8.81 τ . If, in triacetylkorsine, one of the acetyl groups were located at C₇, in korsinone the signal from the 19-methyl group should be displaced to a weaker field; a carbonyl group in position 7 is deshielded almost four times more strongly by a 19-methyl group than one in position 11. Consequently, the third hydroxy group in korsine is located at C₁₁ and has the α orientation.

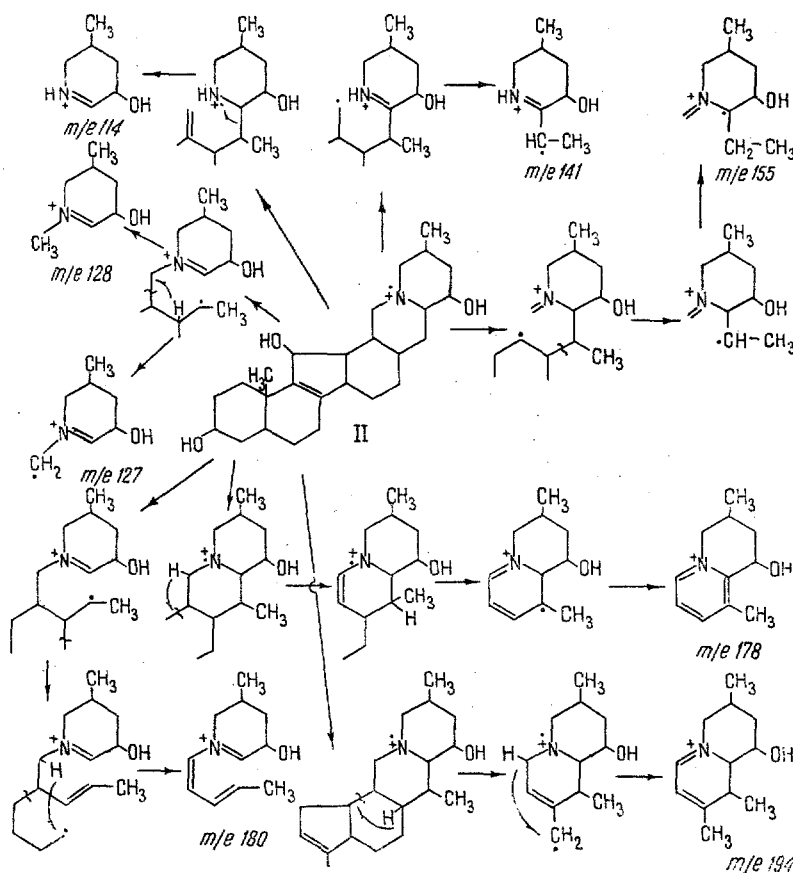
The presence in the IR spectra of korsine and its conversion products of a trans band shows the trans linkage of rings E and F. In the NMR spectra, the signals from the 27-methyl group are considerably shielded. Thus, the 27-methyl group has the α orientation. In the NMR spectra of triacetylkorsine and korsinone, the strengths of the signals from the 27- and 21-methyl groups are similar and they are located at 9.17 τ , which shows the β -conformation of the 21-methyl group.

The hydroxy group at C₂₃, like the hydroxy group at C₁₁, has the α orientation and, accordingly, in the NMR spectrum of triacetyldihydrokorsine signals from the 11 β and 23 β protons are found in the weak field at 5.08 τ .

On the basis of the data presented and the linkage of the configuration of rings A, B with E and F in the stable form, the most probable structure and configuration(II) may be proposed for korsine.

In the mass spectrometry of korsine, the ions mentioned above are formed in the following way. The fragment with m/e 114 is obtained from the molecular ion of korsine (II) by C-N and α -cleavages of bonds with the subsequent migration of hydrogen from C₁₃ to nitrogen and the ion with m/e 127 after α , α -cleavages. The migration of hydrogen from C₁₇ to C₁₈ or C₂₂ leads to the appearance of an ion with m/e 128. The cleavage of C-N and C₁₇-C₂₀ bonds forms an ion with m/e 141, and of the C₁₃-C₁₈ and C₁₇-C₂₀ bonds a fragment with m/e 155.

In the molecular ion, β -cleavage of a bond with the migration of hydrogen from the α position to C₁₂ and ejection of the non-nitrogenous part of the substance and of the hydrogens from C₂₀ and C₂₂ forms an ion with m/e 178. α,γ -cleavages with the migration of hydrogen from C₁₈ to C₁₆ and subsequent cleavage of the C₁₂-C₁₃ bond lead to a fragment with m/e 180. If, after β -cleavage, the migration of hydrogen takes place from C₁₇ to C₁₂, further cleavage takes place at the C₁₅-C₁₆ bond with the migration of a hydrogen atom from C₁₈ to C₁₆ and the formation of an ion with m/e 194. The fragment with m/e 358 (M - 71) is obtained by the cleavage of the C₂₂-C₂₃ and C₂₅-C₂₆ bonds with the migration of hydrogen from C₂₄ to C₂₆. The ion with this mass number may arise in part after the cleavage of the C₄-C₅ bond with the migration of hydrogen from C₃ to C₄ and from C₂ to C₅ and cleavage of the C₁-C₂ bond. The fragment with m/e 372 (M - 57) is obtained after the ejection of fragments as a consequence of cleavages of the C₁-C₁₀ and C₃-C₄ bonds and the migration of hydrogen from C₂ to C₄. The ion with m/e 384 (M - 45) is formed after the elimination of an oxygen-containing fragment from ring F and, in part, from ring A.



Experimental

The bulbs of *Korolkowia sewerzowii* (38 kg) collected in the Chatkal Valley in the stage of the dying off of the epigeal part were extracted by the usual chloroform method. This gave 304 g (0.8%) of total alkaloids. The mixture of bases was separated with respect to their solubility in petroleum ether (34.06 g), ether (174.8 g) and chloroform (95.14 g). From the 34.06 g, korsevine was isolated [3, 4]. The 174.8 g was separated with respect to basicity into 20 fractions. From the first five fractions, after treatment with benzene, a mixture of crystals was obtained which, on standing in methanol, gave korsine with mp 236–238° C (from methanol), 257–259° C (from ethanol), or 259–260° C (from acetone). All the melting points remained constant on repeated recrystallization from the solvents mentioned and after drying at 100° C in vacuum (3–5 mm). The IR spectra of all three types of crystals differed from one another. Korsine loses solvent at 170° C in vacuum (3–5 mm) and has mp 257–259° C. IR spectrum: ν_{\max} 3490, 3420, 1090, 1056, 1010 (OH), 2780 (trans-quinolizidine) [18], 2930–2830, 1485–1465 (C–CH₃), 1670 cm⁻¹ (C=C), $[\alpha]_D^{+87.9}$ (c 0.1; ethanol), R_f 0.3 (in a thin fixed layer of Al₂O₃). Solvent system: 1) butyl acetate–chloroform–ethanol (25:25:4). The Kuhn-Roth oxidation of korsine gave 2.7 moles of acetic acid.

Found, %: C 75.65, 75.48; H 10.08, 10.10; N 3.18, 3.15; mol. wt. 429 (mass spectrometry). Calculated for C₂₇H₄₃O₃N, %: C 75.52; H 10.02; N 3.26; mol. wt. 429.

Korsine is readily soluble in ethanol, moderately soluble in methanol and acetone, sparingly soluble in chloroform, pyridine, carbon tetrachloride, and carbon disulfide, and insoluble in water.

Korsine hydrochloride has mp 301–303° C (from acetone); the hydrobromide mp 324–326° C (from acetone), and the hydriodide mp 292–294° C (from acetone).

Methiodide. Formed by boiling the base with methyl iodide in methanol for 1 hr, mp 273–275° C (from acetone).

Triacetylkorsine. A mixture of 0.2 g of korsine, 4 ml of pyridine, and 3 ml of acetic anhydride was left at 30° C for 3 days. Triacetylkorsine perchlorate was obtained with mp 290–292° C (from acetone).

Found, %: C 58.47, 58.62; H 7.67, 7.50; N 2.09, 2.20. Calculated for C₃₃H₄₉O₆N · HClO₄, %: C 60.41; H 7.53; N 2.15.

From the perchlorate, triacetylkorsine was obtained in the form of a powder with R_f 0.84 (1). IR spectrum ν_{\max} 1028, 1250, 1745 cm⁻¹; NMR spectrum: singlets at 8.02 τ (3H, COOCH₃) and 8.05 τ (6H, 2 COOCH₃). Saponification of the triacetylkorsine gave the initial alkaloid.

Dihydrokorsine. In the presence of a platinum catalyst (from 0.1 g of PtO_2), a solution of 0.2 g of the base in 20 ml of 10% acetic acid was shaken in an atmosphere of hydrogen. Dihydrokorsine with mp 274–276° C (from methanol), R_f 0.16 (1), was formed.

Triacetyldihydrokorsine was obtained in the same way as triacetylkorsine, mp 235–236° C (from acetone), R_f 0.82 [butyl acetate–chloroform–methanol (25:25:3)].

Korsinone. A mixture of 0.3 g of korsine in 12 ml of glacial acetic acid and 0.15 g of chromic anhydride in 6 ml of glacial acetic acid was heated at 80° C for 30 min.

The korsinone had mp 276–278° C (from methanol), R_f 0.37 (1); IR spectrum: ν_{max} 1700 cm^{-1} ($\text{C}=\text{O}$); UV spectrum: λ_{max} 245, 300 $\text{m}\mu$ ($\log \epsilon$ 2.08, 2.03). Korsinone oxime, obtained by the usual method, had mp 273–275° C (from acetone). Its IR spectrum had no absorption band for a carbonyl group.

Found, %: N 6.53, 6.60. Calculated for $\text{C}_{27}\text{H}_{42}\text{O}_3\text{N}_2$, %: N 6.33.

Korsinedione. A mixture of 0.3 g of korsine in 12 ml of glacial acetic acid and 0.3 g of chromic anhydride in 12 ml of glacial acetic acid was heated at 80° C for 30 min. This gave korsinedione with mp 258–260° C (from acetone); R_f 0.45 (1); IR spectrum: ν_{max} 1725 ($\text{C}=\text{O}$), 1680 ($\text{C}=\text{C}$) cm^{-1} ; UV spectrum: λ_{max} 245, 300 $\text{m}\mu$ ($\log \epsilon$ 2.97, 2.80).

Korsinedione dioxime, obtained by the usual method, had mp 277–278° C (from methanol).

Found, %: N 8.75, 8.72. Calculated for $\text{C}_{27}\text{H}_{41}\text{O}_3\text{N}_3$, %: N 8.84.

Dihydrokorsine from korsinone. In the presence of a platinum catalyst (from 0.1 g of PtO_2), 0.15 g of korsinone in 20 ml of 10% acetic acid was shaken in an atmosphere of hydrogen. Mp 276–278° C. A mixture with dihydrokorsine gave no depression of the melting point, R_f 0.16 (1).

Dihydrokorsinone was obtained by oxidizing dihydrokorsine in the same way as korsinone was prepared from korsine. Mp 218–220° C (from acetone); R_f 0.5 (1). IR spectrum: ν_{max} 1710 cm^{-1} ; UV spectrum: λ_{max} 290 $\text{m}\mu$ ($\log \epsilon$ 1.8).

Dihydrokorsinone oxime had mp 188–191° C (from acetone).

Deoxodihydrokorsinone. 0.22 g of korsinone was reduced by the Huang-Minlon method. Deoxodihydrokorsinone with mp 208–210° C (from methanol) was formed. The IR spectrum had no absorption band of a carbonyl group, R_f 0.56 (1).

The IR spectra were recorded on a UR-10 double-beam spectrophotometer (molded tablets with KBr); the UV spectra on an SF-4 spectrophotometer (ethanolic solutions); the mass spectra on an MKh-1303 mass spectrometer with a glass inlet system at 40 eV and 50 mA; and the NMR spectra (in deuteriochloroform) on a JNM-4H-100 instrument with hexamethyldisiloxane as the internal standard.

Conclusions

A new alkaloid korsine, $\text{C}_{27}\text{H}_{43}\text{O}_3\text{N}$, has been isolated from the bulbs of *Korolkowia sewerzowii*. Its structure and configuration have been established on the basis of a study of its chemical properties and IR, UV, NMR, and mass spectra.

REFERENCES

1. S. Yu. Yunusov, R. A. Konovalova, and A. P. Orekhov, *ZhOKh*, 9, 1911, 1939.
2. G. Kittel and A. S. Sadykov, *DAN UzSSR*, 1, 11, 1948.
3. R. N. Nuriddinov and S. Yu. Yunusov, *DAN UzSSR*, 3, 40, 1966.
4. R. N. Nuriddinov and S. Yu. Yunusov, *KhPS [Chemistry of Natural Compounds]*, 3, 398, 1967.
5. T. T. Chu and W. K. Hwang, *Acta Chim. Sin.*, 24, 345, 1958.
6. R. Shakirov, R. N. Nuriddinov, and S. Yu. Yunusov, *Uzb. khim. zh.*, no. 1, 38, 1965.
7. H. Budzikiewicz, *Tetrah.*, 20, 2267, 1964.
8. R. N. Nuriddinov, R. Shakirov, and S. Yu. Yunusov, *KhPS [Chemistry of Natural Compounds]*, 3, 314, 1967.
9. R. F. Zürcher, *Helv. Chim. Acta*, 46, 2054, 1963.
10. T. Masamune, M. Takasugi, M. Gonda, H. Suzuki, S. Kawahara, and T. Irie, *J. Org. Chem.*, 29, 2282, 1964.
11. T. Masamune, N. Sato, K. Kobayashi, J. Yamasaki, and Y. Mori, *Tetra.*, 23, 1591, 1967.
12. T. Masamune, Y. Mori, M. Takasugi, and A. Murai, *Tetrah. Let.*, 16, 913, 1964.

13. T. Masamune, M. Takasugi, and Y. Mori, *Tetrah.*, 9, 489, 1965.
14. S. Ito, I. B. Stothers, and S. M. Kupchan, *Tetrah.*, 20, 913, 1964.
15. I. W. Apsimon, W. G. Craig, P. W. Demarco, D. W. Matieson, L. Saunders, and W. B. Whalley, *Tetrah.*, 23, 2357, 1967.
16. A. R. H. Cole, R. N. Jones, and K. Dobriner, *J. Amer. Chem. Soc.*, 74, 5571, 1952.
17. J. Tomko, L. Voticky, H. Budzikiewicz, and L. J. Durham, *Coll.*, 30, 3320, 1965.
18. K. Nakanishi, *Infrared Spectra and the Structure of Organic Compounds* [Russian translation], Moscow, p. 48, 1965.

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