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STRUCTURE OF BUCHARAINE

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The alkaloids skimmianine, folifine, haplopine, and the new base bucharaine have been isolated previously from the epigeal part of Haplophyllum bucharicum Litv. [1, 2].

Bucharaine, $C_{19}H_{25}O_4N$, is soluble in ethanol and methanol, sparingly soluble in chloroform and acetone, and insoluble in alkalis; it is not methylated by diazomethane. A functional analysis of this substance showed the presence in it of two hydroxyl groups.

Bucharaine gives a dibromo, a N-methyl, and an O-acetyl derivative, and its molecular weight is 331 (mass spectrum).

The IR spectrum of the alkaloid has absorption bands at (cm^{-1}) 3310 (hydroxyl group), 2955 (NH group), and 1675 (amide carbonyl).

The developed formula of bucharaine is $C_{18}H_{22}$(NH) (CO) $(OH)_2$(—O—) (=).

The presence of two alcoholic hydroxyl groups in the alkaloid was confirmed by the preparation of a chloroacetyl derivative the IR spectrum of which lacked the absorption band of a hydroxyl group but contained new bands at 1740 and 1240 cm^{-1} characteristic for alcohol esters. Kuhn-Roth oxidation gave acetone. These facts showed the presence in bucharaine of a CH_3—C(OH)—CH_3 grouping.

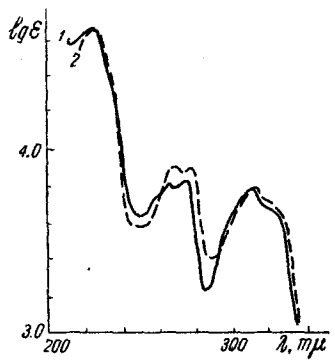
The UV spectrum of bucharaine is very similar to that of 2,4-dihydroxyquinoline (figure).

Hydrogenation of the alkaloid with a platinum catalyst takes place with the cleavage of an ether bond [5] and the formation of two fragments: a nitrogen-free oily substance A with the composition $C_{10}H_{22}O_2$, and substance B with mp 354-356° C. The latter was also obtained by the action of alkyl halides and halogen acids on bucharaine.

A direct comparison of the methyl ether and nitroso and acetyl derivatives of substance B with the analogous derivatives of 2,4-dihydroxyquinoline showed their identity.

Consequently, bucharaine has a 2,4-dihydroxyquinoline structure in which the γ-position is substituted by a $C_{10}H_{19}O_2$ residue.

The ozonolysis of bucharaine yielded bucharainic acid $C_{17}H_{21}O_6N$, with mp 288-289° C, and acetaldehyde, which shows the presence of a double bond at the end of a chain in the form —C=CH—CH_3.



UV spectra of bucharaine (1) and of 2,4-dihydroxyquinoline (2).

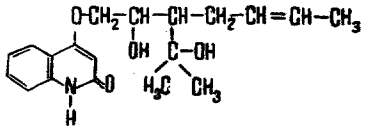
The nitrogen-free substance A was oxidized by Percheron's method [6, 7] and the volatile acids were trapped. Acetic and valeric acids were detected by paper chromatography. The formation of valeric acid shows that the hydroxyisopropyl grouping is present on carbon atom 5 of the side chain of bucharaine.

In the region of low mass numbers in the mass spectrum, very strong peaks of ions with m/e 55 and 41 are observed the formation of which can be explained by the assumption that bucharaine has a chain with branching at the fifth carbon atom [8].

The NMR spectrum of bucharaine has a singlet at δ 6.87 ($H_{(3)}$ proton), a multiplet with a center at δ 7.42 ($H_{(6,7,8)}$ protons), and a quadruplet at δ 7.88 ($H_{(5)}$ proton).

In the region of the signals of aliphatic protons there is a one-proton quadruplet with δ 3.59, the chemical shift of which corresponds to a proton adjacent to a hydroxyl group [9], and a doublet (δ = 4.6, J = 6 Hz) with an intensity of 2 proton units. These two signals may be caused [10] by a CH_2—CH(OH) group. The position of the signal of the methylene group is characteristic for groups adjacent to an oxygen atom attached to the nucleus [11], O—CH_2—CH(OH)—.

The three-proton signal at δ 1.63 can be ascribed to methyl protons, and the broadened two-proton peak at δ 1.19 is probably caused by hydroxyl protons. The signals of the two methyl groups (δ 1.36, 1.38) are split by 2 Hz. This splitting is due to the interaction of the methyls with the hydroxyl proton of the hydroxypropyl group. Consequently, bucharaine has the structure



Experimental

The alkaloids were extracted from the air-dried comminuted raw material with chloroform in a continuous apparatus.

In the flowering period the epigeal part of the plants contained 0.47% of alkaloids—the leaves separately 0.56% and the roots 0.06%. Bucharaine deposited from the five-fold concentrated chloroform extract. The residual mixture of alkaloids with different solubilities in acid yielded the hydrochloride of the base, and then skimmianine and folifine. In addition, the ethereal fraction, by chromatography on alumina, yielded haplopine.

Bucharaine forms white crystals with mp 151–152° C. On a nonfixed thin layer of Al_2O_3 in the ethyl acetate–methanol (9 : 1) system, it gives a single spot with R_f 0.54 (revealed with iodine).

Found, %: C 68.59; H 7.62; N 4.09; mol. wt. 330.9 (Rast.) and 331 (mass spectroscopy). Calculated for $C_{19}H_{25}O_4N$, %: C 68.85; H 7.60; N 4.20; mol. wt. 331.3.

Dibromo derivative. Two grams of bucharaine was added slowly to 25 ml of a 3% ml chloroform solution of bromine. The alkaloid first dissolved, and on standing a precipitate of the dibromo derivative with mp 145–146° C (from acetone) deposited (2.8 g).

Found, %: Br 31.95. Calculated for $C_{19}H_{25}O_4Br_2N$, %: Br 32.6.

Nitro derivative. With cooling, 0.4 g of the base was dissolved in 6 ml of conc H_2SO_4, and then 3 ml of conc HNO_3 was added in portions. The mixture was poured into 80 ml of water containing ice. Yellow crystals with mp 168–169° C (from methanol) deposited.

Found, %: C 61.6; H 6.63; N 7.13. Calculated for $C_{19}H_{25}N_2O_6$, %: C 60.46; H 6.67; N 7.42.

Acetylation of bucharaine with acetyl chloride. A mixture of 1 g of bucharaine and 15 ml of acetyl chloride was left for 8 days, after which the excess of acetyl chloride was eliminated by evaporation. The residue contained chlorine which was not removed by treatment with ammonia. Mp 164–165° C (from methanol).

Monoacetyl derivative of bucharaine. A solution of 3 g of bucharaine in 30 ml of acetic acid and 6 ml of acetic anhydride was heated at 100° C for 8 hr. The crystals of monoacetylbucharaine that deposited after cooling had mp 164–165° C (from acetone).

The saponification of acetylbucharaine with 20% ethanolic caustic potash yielded bucharaine.

Found, %: C 67.61; H 7.53; N 3.37. Calculated for $C_{21}H_{27}NO_5$, %: C 67.52; H 7.29; N 3.77.

Oxidation of bucharaine with chromic acid. Bucharaine (1 g) was added to a mixture of 10 g of chromic anhydride, 10 ml of concentrated sulfuric acid, and 40 ml of water. The resulting mixture was heated for 2 hr, and the acetone was trapped with a 0.1% hydrochloric acid solution of 2,4-dinitrophenylhydrazine. A mixture of the hydrazone that deposited (mp 124–125° C) with acetone, 2,4-dinitrophenylhydrazone gave no depression of the melting point.

Hydrogenation of bucharaine. A solution of 2 g of bucharaine in 100 ml of ethanol was shaken in a current of hydrogen with a platinum catalyst prepared from 0.1 g of platinum oxide. In 3 hr, 272 ml of hydrogen was absorbed. When the ethanolic solution was concentrated, crystals of 2,4-dihydroxyquinoline with mp 355–356° C (from ethanol) deposited.

Found, %: C 67.85; H 5.02; N 8.66. Calculated for $C_9H_7O_2N$, %: C 67.07; H 4.87; N 8.69.

The ethanolic mother liquor was treated with 50 ml of water and distilled with steam. The distillate was extracted with ether and the ether was distilled off to leave an oily nitrogen-free residue.

Found, %: C 68.1; H 12.6. Calculated for $C_{10}H_{22}O_2$, %: C 68.3; H 12.72.

Acetylation of 2,4-dihydroxyquinoline. A mixture of 0.15 g of the substance, 3 ml of acetic anhydride, and two drops of pyridine was heated for 2.5 hr. The crystals that deposited after cooling had mp 212–213° C. There was no depression in admixture with the acetyl derivative of 2,4-dihydroxyquinoline.

Methylation of 2,4-dihydroxyquinoline. An ethereal solution of diazomethane was added to a suspension of 0.2 g of the substance in ether, and the mixture was left for 5 days. Crystals with mp 244° C deposited. A mixture with the methyl ether of 2,4-dihydroxyquinoline showed no depression of the melting point.

Nitroso derivative of 2,4-dihydroxyquinoline. A mixture of 0.2 g of the substance and 0.08 g of sodium nitrite was dissolved in 4% caustic soda. With cooling, the solution was acidified with 10% H_2SO_4. The red precipitate of nitroso derivative with mp 204–205° C (from glacial acetic acid) that deposited was identical with an authentic sample.

Action of methyl iodide on bucharaine. A mixture of 3 g of bucharaine, 6 ml of methyl iodide, and 10 ml of methanol was heated in a sealed tube for 2 hr. This led to the deposition of 1.42 g of 2,4-dihydroxyquinoline, giving no depression of the melting point with an authentic sample.

N-Methylbucharaine. A mixture of 1 g of bucharaine, 9 ml of methyl iodide, 4.5 g of anhydrous potassium carbonate, and 300 ml of dry acetone was heated for 6 hr. When the filtrate was concentrated, a crystalline precipitate deposited with mp 142–143° C (from ethanol).

Found, %: N–CH_3 4.25. Calculated for $C_{20}H_{27}NO_4$, %: N–CH_3 4.5.

Ozonolysis of bucharaine. A current of ozone was passed into a solution of 1 g of bucharaine in 200 ml of absolute dioxane at 0° C. Then the dioxane was distilled off under vacuum and the residue was treated with 5% sodium carbonate solution. The sodium carbonate solution was acidified with 10% HCl. Bucharainic acid with mp 288–289° C (from ethanol) deposited.

Found, %: C 61.5; H 6.46; N 4.35. Calculated for $C_{17}H_{21}O_6N$, %: C 60.9; H 6.3; N 4.17.

Bucharaine (50 mg) was oxidized with ozone in absolute dioxane. The dioxane was distilled off under vacuum at room temperature and the residue was treated with 50 ml of ice water and distilled with steam. The distillate was collected in a hot 1% solution of dimedone. Acetaldehyde in the form of the dimedone acetal was isolated.

The NMR spectrum was recorded in a JNM-100/100 MHz instrument in deuteropyridine with tetramethylsilane as internal standard. The values are given in the δ scale.

Conclusions

From the plant Haplophyllum bucharicum Litv. have been isolated skimmianine, folifine, haplopine, and a new base, bucharaine.

Bucharaine has the structure 4-(6'-hydroxy-5'-hydroxyisopropylhept-3'-enyloxy)quinol-2-one.

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