ALKALOIDS OF Haplophyllum pedicellatum, H. obtusifolium, AND H. bucharicum. STRUCTURE OF BUCHARAMINE

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The isolation of γ-fagarine and skimmianine from the epigeal part of H. pedicellatum Bge. has been reported previously [1]. We have investigated this plant collected in the environs of Dekhkanabad, Uzbek SSR, on June 3, 1964, in the flowering stage. The methanolic extraction of the epigeal part of the plant gave the combined alkaloids, from which skimmianine, γ-fagarine, haplopine [2], and robustine [3] were isolated.

The plant H. obtusifolium Ldb. was collected in the region of Kora-Kola, Turkmenian SSR, in the flowering stage (June 2, 1970). Chloroform extraction of the epigeal part of the plant gave a mixture of bases, from which skimmianine and evoxine [2] were isolated.

In the mother liquors of the combined alkaloids of H. bucharicum Litv. remaining after the separation of the bucharaine, skimmianine, haplopine, folifine [4] and bucharidine [5] we found γ-fagarine, robustine, and benzamide. From the mother liquors obtained in the recrystallization of bucharaine we isolated a base with mp 223°C, mol. wt. 371 (mass spectrometry). The alkaloid is optically inactive, readily soluble in methanol and chloroform, crystallized from acetone, and is insoluble in water and alkalis, while it dissolves in acids on gentle heating. The base proved to be new and we have called it bucharamine.

Bucharamine lacks methoxy, methylenedioxy, and N-methyl groups. The IR spectrum of the substance shows bands at 1504, 1518, 1575, and 1625 cm^{-1} of approximately equal intensities, which is characteristic for 2-alkoxyquinolin-4-ones [6]. The UV spectrum of the base [λ_{max} 215, 233, 250 (inflection), 298 (inflection), 306, and 318 nm; log ε 4.19, 4.24, 3.96, 3.69, 3.78, and 3.71] is close to that of folisine, which has a dihydropyranoquinolin-4-one skeleton [7]. The absence from the UV spectrum of a maximum in the 265-295 nm region, and also the change in the spectrum on acidification, is characteristic of quinolin-4-ones [8].

In the weak-field region the NMR spectrum of the alkaloid has a one-proton resolved doublet at τ 1.63 (H_5) and a three-proton multiplet at 2.53 ($H_{6,7,8}$) showing the absence of substituents in the benzene ring of the quinoline nucleus. The shift of the H_5 signal by 90 Hz downfield relative to the center of the multiplet of the other aromatic protons confirms the 2-alkoxyquinolin-4-one structure of bucharamine. The spectrum contains two one-proton signals in the form of broad unresolved multiplets at 5.4 and 6.4 ppm (α-proton of a dihydrofuran ring and $-CH-O-$) and a 22-proton signal at 7.65-9.2 ppm including six $C-CH_3$ groups. Since the molecular weight of bucharamine differs from that of bucharaine and bucharidine [5] by 40 mass units, we assumed that the base isolated contains an acetonide group.

The acid hydrolysis of bucharamine formed a substance (II) with mp 206°C, mol. wt. 313 (mass spectrometry), and acetone was found in the volatile fraction of the hydrolyzate, being identified in the form of the 2,4-dinitrophenylhydrazone. The difference of 58 units of the molecular weight of (II) from that of the initial substance shows that in addition to the saponification of the acetonide a pinacolone rearrangement of the resulting diol took place. This is confirmed by the IR and mass spectra. The IR spectrum of (II) lacks

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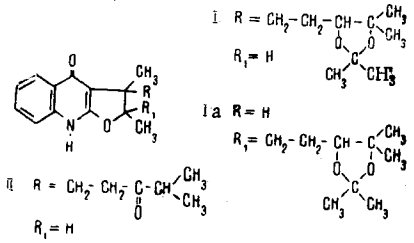
the absorption band of a hydroxy group but it has an absorption band at 1710 cm^{-1} of a carbonyl group. The main peaks in the mass spectrum of bucharamine (I) are: 371 (M^+, 3%), 365 (6%), 313 (30%), 215 (80%), 214 (100%), 200 (19%), and in the saponification product (II) 313 (M^+ 10%), 215 (75%), 214 (100%), 200 (18%). The spectrum of (II) also has peaks with m/e 270 and 242 of low intensity (2.5 and 5%, respectively), formed as the result of the cleavage of bonds in the α position to a carbonyl group. In both substances, the maximum peak arises on the detachment of R from the quaternary carbon atom.

On the basis of what has been said above, and also the biogenetic relationships of bucharamine with bucharaine and bucharidine [5] (all three alkaloids contain an unsubstituted dihydroxyquinoline nucleus and two isoprene units), two possible structures can be put forward for the base: (I) and (Ia).



However, the presence in the NMR spectrum of (II) of a quartet at 5.46 ppm (J=6.5 Hz), the chemical shift and spin–spin coupling constant of which are typical for the α-proton of a dihydrofuran ring [9], permits us to consider structure (I) as the more likely.

Thus, bucharamine is the acetonide of the product of linear condensation of the normal Claisen rearrangement of bucharaine. A similar alkaloid, but with one isoprene unit, has been isolated from the plant Flindersia ifflaina F. Muell [10].

By chloroform extraction, the roots of H. bucharicum collected in the budding stage (May 8, 1962, in the environs of Dekhkanabad) have yielded alkaloids from which skimmianine, dyctamnine, γ-fagarine, haplopine, robustine, and a small amount of bucharaine have been isolated. All the alkaloids were identified by direct comparison with authentic samples (by mp, IR spectra, and TLC).

Consequently, unlike the epigeal part, from which, in addition to furanoquinoline alkaloids, alkaloids forming derivatives of 4-alkoxyquinolin-2-one and 2-alkoxyquinolin-4-one have been isolated as the main products, the roots contain furanoquinoline bases and only traces of bucharaine.

EXPERIMENTAL

H. pedicellatum Bge. The epigeal material (7 kg) was extracted with methanol. The concentrated extract was treated with 10% sulfuric acid. The acid solution was partially neutralized to a feebly acid reaction and was passed through KU-2 anion-exchange resin. The alkaloids were desorbed by ammoniacal methanol. The yield of the mixture of bases was 28 g (0.4%). When the mixture was treated with acetone, 9.9 g of skimmianine separated out. The mother liquors were chromatographed on alumina. The ethereal eluates yielded 11 g of γ-fagarine and 0.6 g of skimmianine, and the ether–chloroform eluates yielded 0.2 g of haplopine. The mother liquors after the removal of the haplopine were separated preparatively in a fixed layer of silica gel, giving robustine.

H. obtusifolium Ldb. The chloroform extraction of 14 kg of the plant gave 6 g (0.04%) of total alkaloids, which were chromatographed on alumina. The ethereal eluates yielded skimmianine and evoxine.

H. bucharicum Litv. The mother liquors remaining after the separation of the bucharaine, skimmianine, haplopine, folifine, and bucharidine were separated into phenolic and nonphenolic fractions. The acetone treatment of 15.2 g of the nonphenolic fraction yielded 5.5 g of skimmianine. The mother liquors were chromatographed on alumina, and the ethereal eluates gave 1.2 g of skimmianine, 0.15 g of γ-fagarine, and 0.3 g of benzamide with mp 122°C, mol. wt. 121 (by mass spectrometry).

Bucharamine. The methanolic mother liquors obtained as the result of the purification of the bucharaine were condensed and chromatographed on alumina. The acetone eluates yielded bucharamine with mp 223°C (from methanol and acetone).

Hydrolysis of Bucharamine. A mixture of 40 mg of the base and 2 ml of 5% sulfuric acid was heated in the sand bath for 45 min. The volatile fraction was trapped with a 0.1% solution of 2,4-dinitrophenylhydrazine hydrochloride. The orange crystals that precipitated had mp 119-120°C and gave no depression of the melting point in admixture with acetone 2,4-dinitrophenylhydrazone. The acid solution was made alkaline with ammonia and extracted with ether. The ether was evaporated off, and the solution deposited crystals with mp 205-206°C (from ether). The substance was readily soluble in the usual organic solvents apart from petroleum ether. On TLC in the methanol–benzene (1:4) system it gave a single spot.

Roots of H. bucharicum. The chloroform extraction of 8 kg of the roots yielded 12 g (0.15%) of the combined bases, from which, by acetone treatments, 7.5 g of skimmianine was isolated. The mother liquor was evaporated and the residue was treated with ethanol. Crystals of robustine (1.4 g) deposited. The remainder of the total alkaloids was passed through a column of alumina. Ethereal eluates yielded 0.15 g of dyctamnine, 0.4 g of skimmianine, and 0.1 g of γ-fagarine, the chloroform eluates yielded 0.08 g of haplopine, and chloroform–methanol eluates yielded 0.005 g of bucharaine.

SUMMARY

1. Haplopine and robustine have been obtained from the epigeal part of H. pedicellatum Bge. and skimmianine and evoxine have been obtained from H. obtusifolium Ldb.

2. The mother liquors of the combined alkaloids from the epigeal part of H. bucharicum Litv. have yielded γ-fagarine, benzamide, and a new base, bucharamine.

3. Bucharamine is an α,β-substituted derivative of α,β-dihydrofuranoquinolin-4-one.

4. The roots of H. bucharicum contain six known alkaloids: dyctamnine, skimmianine, γ-fagarine, robustine, haplopine, and bucharaine.

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