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Berberis ALKALOIDS.

THE NEW ALKALOID OBLONGAMINE

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Continuing a study of the alkaloid composition of some species of *Berberis*, we have investigated young shoots of *B. integerrima*, collected in July, 1974, in Kirghizia in the fruit-bearing phase and of *B. oblonga*, collected in May, 1975, in the Tashkent oblast in the flowering phase.

The total amount of tertiary bases from *B. integerrima* was 0.17%. When they were separated on a column of silica gel, berbamunine (I), identified by comparison with physical constants and spectra with those given in the literature [1], was obtained. In the study of about 50 species of barberry, only one species, *B. amurensis* [2] yielded berbamunine. A second alkaloid isolated from the tertiary bases of *B. integerrima* was hydroxyacanthine (II).

From the combined quaternary bases we isolated, in the form of iodides, 0.35% of magnoflorine and 0.11% of berberine.

The amount of tertiary bases in *B. oblonga* was 0.33%. From them we isolated substances (I) and (II). The combined quaternary bases yielded 0.6% (on the weight of the raw material) of berberine, magnoflorine, and palmatine iodides. The bases were identified by comparison with authentic samples.

A comparison of the alkaloid compositions of the roots [3], leaves [4], and the stems of *B. integerrima* and *B. oblonga* showed that in spite of the absence of substance (I), from the roots, the combined alkaloids of the roots and stems were qualitatively similar while the mixture of bases in the leaves differed greatly.

Continuing the separation of the combined tertiary bases from the roots of *B. oblonga* [3], we isolated a new alkaloid in the form of an iodide with mp 198-200°C, which we have called oblongamine (III). UV spectrum: $\lambda_{\max}^{\text{ethanol}}$ 284 nm (log ε 3.97). The mass spectrum of (III) had peaks with m/e 622, 607, 577, 564, 550, 501, 411, 396, 395, 381, 220, 206, 198, 175, 174, 58 (100%). The NMR spectrum of oblongamine taken in deuteropyridine showed the signals of $N{-}CH_3$, $\overset{+}{N}{-}(CH_3)_2$, and three OCH_3 groups at 3.1, 3.15, 3.31, and 3.61 ppm, respectively; and of 10 aromatic protons in the 6.39-7.0 ppm region. These facts show that (III) belongs to the group of monoquaternary dimeric bisbenzylisoquinoline alkaloids [5]. Judging from the mass spectrum, (III) must be assigned to the hydroxyacanthine type. Since the methiodide of (III) (IV) differed from the dimethiodide of hydroxyacanthine (V) not only by its melting point but also by its R_f value, we performed a Hofmann degradation of (IV) and isolated two des bases: A and B. Correspondingly, (V) yielded A' and B'. Products A and A' proved to be identical (TLC, IR). Thus, the methiodides (IV) and (V) must be diastereomers and the nature of the heterocyclic skeleton and the positions of the hydroxy and methoxy groups and of the oxygen bridges in oblongamine have been shown.

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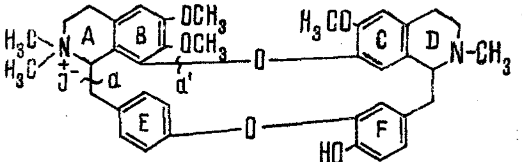
The question of which of the nitrogen atoms — in ring A or ring D — is quaternary was solved through the mass spectrum [6]. The peak of an ion with m/e 220 could arise by the cleavage *aa'* with the migration of H to rings A and B only if the N-dimethyl group were in ring A. There is no ion with m/e 220 in the spectrum of hydroxyacanthine. Consequently, the most probably structure (III) may be proposed for oblongamine:



III

Oblongamine is the first monoquaternary base of the hydroxyacanthine type.

We have previously reported the isolation of a quaternary alkaloid (VI) from the roots of *B. oblonga* [7]. A direct comparison of the product of the reduction of (VI) and carypalline [8] show their identity. Thus, (VI) is a 7-hydroxy-6-methoxy-2-methylisoquinolinium or 7-hydroxy-6-methoxy-2-methyldihydroisoquinolinium salt.

EXPERIMENTAL

The UV spectra were taken in ethanol on a Hitachi spectrophotometer, the IR spectra on a UR-20 instrument (tablets of KBr), the mass spectra on an MKh-1303 instrument with direct introduction of the sample at 160-190°C at an ionizing voltage of 40V, and the NMR spectra on a KNM-4H 100/100 MHz instrument. The melting points are uncorrected.

Isolation of the Combined Alkaloids from *B. integerrima*. Berberine and Magnoflorine Iodides. The air-dried comminuted raw material (4.2 kg) was wetted with 5% sodium carbonate solution and extracted with chloroform (five times). The combined extracts were concentrated to 2 liters and treated with 10% sulfuric acid. The acid solution was washed with ether and chloroform and it was then made alkaline with 25% NH_4OH and was reextracted with ether and chloroform. The ethereal chloroform extracts gave 4 g and 3.21 g, respectively, of mixtures of bases.

The raw material after extraction with chloroform was reextracted with methanol (five times). The methanol was evaporated in vacuum to a syrupy mass, and this was triturated with 10% sulfuric acid. The acid solution was washed with ether, and then crystalline KI was added. Berberine iodide (4.62 g) precipitated first, and then brown resin deposited. After a day, the acid solution was decanted off, the resin was washed with water and dissolved in methanol, and from the solution was crystallized 14.7 g of magnoflorine iodide.

The isolation and separation of the combined alkaloids from *B. oblonga* was performed in a similar manner. From 0.5 kg of raw material were obtained 1.23 g of combined ether-soluble bases, 0.45 g of combined chloroform-soluble bases, and 3 g of combined quaternary iodides, from which magnoflorine, berberine, and palmatine iodides were isolated by recrystallization from methanol.

Isolation of Hydroxyacanthine (II). The combined ether-soluble bases of *B. integerrima* (1 g) were separated on a column containing 50 g of silica gel. On elution with a mixture of chloroform and methanol (97:3), a crystalline base with mp 206-208°C (ethanol), and the dimethiodide (V) of (II), with mp 260-265°C, were isolated. The base was identified as hydroxyacanthine by comparison with an authentic sample.

Isolation of Berbamunine (I). When chloroform—methanol (95:5) was passed through the column it eluted a crystalline base with mp 190-191°C (acetone), $[\alpha]_D$ +55° (c 0.5; chloroform); UV spectrum: $\lambda_{max}^{ethanol}$ 283 nm (log ε 4.02). NMR (δ scale): 3.74 (6H, s, 2 OCH_3), 2.35 (3H, s, $N—CH_3$), 2.40 (3H, s, $N—CH_3$), 6.05-7.00 (11H, m, Ar—H); mass spectrum: m/e 192 (100%), 178 (see [9]).

Methiodide of the Trimethyl Ether of (I). A mixture of 0.3 g of (I), 5.6 ml of 0.5 N methanolic KOH, and 0.5 ml of CH_3I was heated for 2H. On cooling, crystals with mp 180-182°C deposited.

A similar separation of the combined bases of the *B. oblonga* also yielded hydroxyacanthine and berbamunine.

Isolation of Oblongamine Iodide (III). A solution of 40 g of the phenolic fraction of the combined tertiary bases [3] in 500 ml of chloroform was washed repeatedly with water, and the combined aqueous extracts were evaporated to dryness. This gave 3.15 g of a mixture of monoquaternary iodides, which were separated on a column containing 150 g of silica gel. Elution with chloroform–methanol (5:3) gave (III).

Oblongamine Iodide Methiodide. (IV). A solution of 0.2 g of (III) in 3 ml of methanol and 0.5 ml of methyl iodide was heated for 1 h. On cooling, (IV) deposited with mp 274-277°C (decomp.).

Hofmann Degradation of (IV). A mixture of 0.2 g of (IV) and 4 ml of 30% methanolic KOH was heated for 2 h. After the solvent had been evaporated off, the residue was dissolved in 10 ml of water, the aqueous solution was saturated with NH_4Cl, and the reaction product was extracted with ether and chloroform. This gave 0.06 and 0.1 g of extracted materials, respectively. The ether-soluble fraction was separated on a column containing 10 g of silica gel. Elution with chloroform–methanol (96:4) yielded 0.01 g of the des base A with mp 206-208°C, $\lambda_{max}^{ethanol}$ 264 nm (log ε 4.48).

The chloroform-soluble fraction (0.1 g) was separated on a column containing 15 g of silica gel. Elution with chloroform–methanol (5:1) gave 0.02 g of the des base B, mp 199-202°C, $\lambda_{max}^{ethanol}$ 285 nm (log ε 4.12).

The Hofmann degradation of (V) was performed in the same way for (IV). 0.5 g of (V) yielded 0.04 g of the des base A'; with mp 210-212°C; $\lambda_{max}^{ethanol}$ 269 nm (log ε 4.41); and 0.05 g of the des base B', mp 202-204°C; $\lambda_{max}^{ethanol}$ 285 nm (log ε 4.02).

The R_f values of A and A' and their mixtures were identical on plates with fixed layers of silica gel in the benzene–methanol (2:1, 1:1) and chloroform–methanol (4:1, 2:1, and 1:1) systems.

SUMMARY

1. The alkaloid compositions of young shoots of *Berberis integerrima* and *B. oblonga* have been studied. Berbamunine, hydroxyacanthine, magnoflorine, berberine, and palmatine have been isolated.

2. The new monoquaternary bisbenzylisoquinoline alkaloid oblongamine has been isolated from the roots of *B. oblonga*.

3. The most probable structure of oblongamine has been suggested on the basis of chemical reactions and spectral characteristics.

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