Berberis ALKALOIDS

2'-N-METHYLBERBAMINE FROM *Berberis oblonga*

A. Karimov, M. V. Telezhenetskaya,
K. L. Lutfullin, and S. Yu. Yunusov

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Continuing the separation of the combined tertiary bases from the roots of *Berberis oblonga* [1, 2], we have isolated a new phenolic alkaloid (I), which is amorphous, in the form of the iodide. $\lambda_{max}^{ethanol}$ 282 nm (log ε 3.87).

The mass spectrum of (I) has the peaks of ions with m/e 622 (M – HI), 608 (M – CH_3I) 417, 396, 395, 361, 198, 175, 174, 142, 127, and 58 (100%). Consequently, (I) is a monotertiary bisbenzylisoquinoline base containing a phenolic hydroxyl in the diphenyl oxide moiety [3, 4]. This is confirmed by the NMR spectrum of (I) taken in Py-d_5, which shows signals from N–CH_3, $\overset{+}{N}(CH_3)_2$, from three OCH_3 groups at 2.14 (3H, s), 3.20 (6H, s), 3.35 (6H, s), and 3.57 (3H, s), and from ten aromatic protons in the 6.35-7.10 ppm region.

The iodide (I) was methylated with diazomethane, giving a monomethyl ether (II) with mp 220-222°C (tetrahydrofuran). The mass spectrum of (II) had the peaks of ions with m/e 636 (M – HI), 622 (M – CH_3I), 607, 485, 431, 395, 381, 198, 175, 174, 142, 127, and 58 (100%). The ion with m/e 485 is formed by the ejection of ring E [5], which enables (I) to

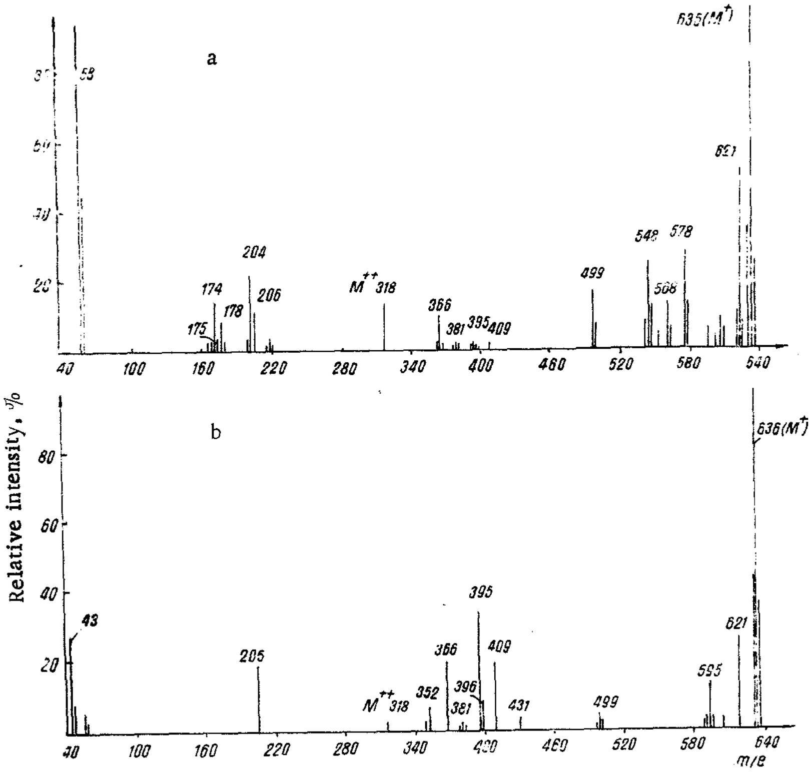

Fig. 1. Mass spectra of the monostilbene (V) (a) and the monostyrene (VI) (b).

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be assigned to the berbamine group. The NMR spectrum of (II) in $CDCl_3$ shows signals from $N{-}CH_3$, $\overset{+}{N}(CH_3)_2$, and four OCH_3 groups at (ppm) 2.15 (3H, s), 3.06 (3H, s), 3.31 (3H, s), 3.55 (3H, s), 3.72 (3H, s), and 3.82 (3H, s) and from ten aromatic protons in the 6.21-6.75 ppm region.

To confirm that one of the nitrogen atoms in (II) and, correspondingly, in (I) is quaternary, we performed the Hofmann degradation of (II). This yielded two des-bases: the monostilbene derivative (V), amorphous, with a yield of ∿60%, and the monostyrene derivative (VI) with a yield of ∿40%. In the mass spectrum of (V) (Fig. 1, a) the strongest peak is that of the molecular ion with m/e 636, and there are ions with m/e 621 (M — 15), 578 (M — 58), and 58, and also an ion with m/e 499 (M — 137), which was formed by the ejection of ring E. In this case, practically no ions formed by dibenzyl cleavage are observed. This is in harmony with the monostilbene structure.

The mass spectrum of (VI) (Fig. 1b) shows the peak of M^+ (m/e 636) and ions formed by dibenzyl cleavage (m/e 395 and 396) and by the ejection of ring E (m/e 499), and also intensive ions with m/e 205 and 44, which characterizes (VI) as a monostyrene base.

Thus, (I) must be a monoquaternary derivative of berbamine or its diastereoisomer. To decide this point, we obtained the methiodide (VII) of (II), the IR spectrum of which proved to be identical with that of the dimethiodide of isotetrandrine (VIII). This defines the configuration of the C-1 and C-1' azometric centers as RS. The choice between the two structures (I) and (III) remains for (I).

Two monoquaternary derivatives of the berbamine type have been described in the literature. The assignment of the signals in the NMR spectra of these bases and of tetrandrine, isotetrandrine, and (II) are given below:

Alkaloid	Absolute configuration	$-OCH_3$				$-CH_3$		Literature
		4″	*6*	*6′*	*7*	*2-N*	*2′-N*	
Tetrandrine*	*SS*	3,90	3,73	3,35	3,18	2,30 3,54	2,59	6
Cycleahomine chloride (IV)†	*SS*	3,94	3,72	3,38	3,30	3,30	2;37 3,48	3
2'-N-Methyltetrandrine (II)†	*SS*	3,91	3,74	3,41	3,26	2,34	3,91	3
Isotetrandrine	*RS*	3,95	3,78	3,63	3,18	2,28	2,60	6
2'-N-Methylisotetrandrine iodide (II)	*RS*	3,82	3,72	3,72	3,31	2,15	3,55 3,06	

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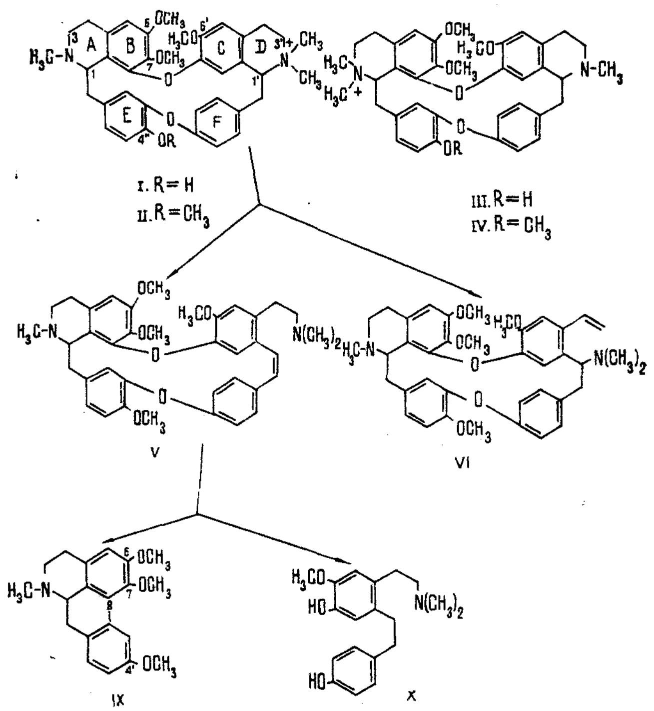
*The spectra of all the bases were taken in $CDCl_3$.

†The assignment of the signals of the methoxy groups has been made by ourselves.

Although the signals of the N-methyl groups in tetrandrine and isotetrandrine differed by approximately 0.3 ppm, it is impossible to conclude that each of these groups is quaternary in cycleahomine chloride (IV) and 2'-N-methyltetrandrine (II), since the values of the signals of the $2{-}N{-}CH_3$ group in (IV) and the $2'{-}N{-}CH_3$ group in (III) are very close. Consequently, we were unable to make a choice between structures (I) and (III) on the basis of the NMR spectrum.

For a definitive answer to this question we undertook the cleavage with sodium in liquid ammonia of the monostilbene derivative (V). Under these circumstances, from the nonphenolic moiety we isolated N-methylarmepavine (IX), which was identified by comparison with an authentic sample, and from the phenolic moiety we isolated a base with (X) with mp 135-137°C the mass spectrum of which showed the peaks of ions with m/e 315 (M^+), 270, 255, 223, 206, 107, and 58 (100%). The PMR spectrum taken in Py-d_5 showed signals from a $N(CH_3)_2$ group (2.82 ppm), an OCH_3 group (3.61 ppm), from benzyl protons (2.61-3.21 ppm), and from aromatic protons (6.90-7.21 ppm). According to its spectral characteristics, the phenol (X) is dihydrode-N-methylcoclaurine. These facts permit the structure of 2'-N-methylberbamine (I) to be assigned to the alkaloid isolated.



EXPERIMENTAL

The UV spectrum was recorded in ethanol on a Hitachi spectrophotometer, the IR spectra on a UR-20 instrument (tablets with KBr), the mass spectra on a MKh-1303 instrument with the direct introduction of the sample at 130-200°C and 40 V ionizing radiation, and the NMR spectrum on a JNM-4H 100/100 MHz instrument. The melting points are uncorrected. The homogeneity of the substances was determined on plates coated with Al_2O_3 in the chloroform–methanol (95:5 and 9:1) systems and on SiO_2 in the chloroform–methanol (9:1, 4:1, and 1:1) systems.

Isolation of 2'-N-Methylberbamine (I). The material from the oblogamine mother liquor [2] (2.2 g) was separated on a column of Al_2O_3 (100 g) by elution with chloroform and with chloroform–methanol. Elution with chloroform–methanol (9:1) yielded 0.35 g of (I).

Preparation of the Methyl Ether (II) of (I). A solution of 300 mg of (I) in 10 ml of absolute methanol was treated with 30 ml of an ethereal solution of diazomethane. After two days, the solvent was driven off and the residue was separated on a column of Al_2O_3 (8 g) with elution by chloroform–methanol (95:5). This yielded 280 mg of (II) with mp 220-222°C (from tetrahydrofuran). $[\alpha]_D$ +29.2° (c 0.16; $CHCl_3$).

Preparation of Methiodide (VII) of (II). A solution of 10 mg of (II) in 2 ml of CH_3OH was treated with 0.1 ml of CH_3I, and the mixture was boiled on the water bath under reflux for 2 h. On standing, the solution deposited crystals of (VII) (10 mg) with mp 244-245°C.

Preparation of (VIII). A solution of 20 mg of berbamine in 3 ml of methanol was treated with 15 mg of Na_2CO_3 and 0.2 ml of CH_3I. The mixture was boiled for 3 h. On cooling, the solution deposited crystals of (VIII) (12 mg) with mp 240-242°C.

Hofmann Degradation of (II). A solution of 240 mg of (II) in 8 ml of 30% methanolic KOH was heated on the water bath for 3 h. After the methanol had been driven off, the residue was dissolved in 20 ml of water and extracted with ether (3 × 100 ml). The ethereal solution was dried over Na_2SO_4, filtered, and evaporated. This gave 200 mg of a mixture of des products.

Isolation of (V) and (VI). The mixture of des products (200 mg) was separated on a column of SiO_2 (10 g) and was washed with chloroform, which gave 70 mg of (VI) with mp 117-119°C. When the column was washed with chloroform–methanol (9:1), 115 mg of (V) was isolated.

Cleavage of (V) with Na/NH_3. A two-necked flask fitted with a stirrer and dropping funnel was charged with 210 ml of dry liquid NH_3 and, with stirring, 0.75 g of metallic sodium was dissolved in it. Then 105 mg of (V) in 20 ml of tetrahydrofuran was added dropwise from the dropping funnel over 45 min. Stirring was continued for another 2 h and the reaction mixture was left overnight. After the liquid NH_3 had been evaporated off, the residue was diluted with 25 ml of water, and the nonphenolic cleavage products were extracted with ether (A). Then the aqueous solution was saturated with NH_4Cl and the phenolic products (B) were extracted with ether.

Isolation of O-Methylarmepavine (IX). A mixture of 55 mg of the nonphenolic cleavage products (A) was chromatographed on a column of SiO_2 (5 g), and chloroform elution yielded (IX) in the form of an oil.

Mass spectrum: 327 (M^+), 206 (100%), 121. NMR in $CDCl_3$: 2.48 ($N-CH_3$); 3.46 ($7-OCH_3$); 3.69 ($4'-OCH_3$); 3.75 ($6-OCH_3$); 5.92 (C_8-H); 6.48 (C_5-H); 6.71 (2H, d), 6.92 (2H, d — four protons of the benzyl moiety.

In its spectral characteristics and R_f values, the product coincided with authentic O-methylarmepavine.

Isolation of Dihydro-de-N-methylcoclaurine (X). A mixture of 45 mg of the nonphenolic cleavage products (B) was separated on a column of SiO_2 (5 g), and elution with chloroform—methanol (4:1) yielded 25 mg of (X) with mp 135-137°C.

SUMMARY

A new alkaloid has been isolated from the roots of *Berberis oblonga*. On the basis of spectral characteristics and chemical transformations, its structure has been determined as 2'-N-methylberbamine.

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