3. A. Karimov, M. B. Telezhenetskaya, K. L. Lutfullin, and S. Yu. Yunusov, Khim. Prir. Soedin., 419 (1978).
4. R. W. Doskotsch, P. L. Schiff, and J. L. Breal, Lloydia, 32, 29 (1969).
5. M. Shamma and J. L. Moniot, Isoquinoline Alkaloids Research, Plenum Press, New York (1978), p. 27.
6. T. Kametani and K. Ohkub, Tetrahedron Lett., No. 48, 4317 (1965).
7. F. N. Allen, O. Kennard, and D. G. Watson, J. Chem. Soc., Perkin Trans. II, S1-S19 (1987).
8. K. Nakanishi, Infrared Spectroscopy. Practical, Holden-Day, San Francisco (1962).
9. Yu. M. Mil'grom, Ya. V. Rashkes, G. V. Fridlyanskii, and B. M. Voronin, Khim. Pri. Soedin., 488 (1990).
10. G. M. Sheldrickk, SHELXS-86 Program for Crystal Structure Determination, Göttingen, FRG.
11. G. M. Sheldrickk, SHELX-76 Program for Crystal Structure Determination, Cambridge, UK.

Berberis ALKALOIDS.

XXII. INTEBRININE AND INTEBRIMINE – NEW ALKALOIDS FROM Berberis integerrima

A. Karimov, V. I. Vinogradova,
and R. Shakirov

UDC 547.944/945

The known alkaloids reticuline, isoboldine, isocorydine, glaucine, armepavine, oxyacanthine, and heliamine and the new alkaloids intebrinine and intebrimine have been isolated from the total alkaloids of the leaves of Berberis integerrima, and structures have been proposed for the latter two on the basis of spectral characteristics and independent synthesis.

The alkaloid composition of the leaves of Berberis integerrima Bge gathered in the environs of Sarikurgana (Fergana province) has been investigated. The new N-benzylisoquinoline alkaloid intebrine has been isolated from the leaves of this plant previously [1]. Chloroform extraction of the leaves yielded 0.28% of total alkaloids (0.19% of ether fraction and 0.09% of chloroform fraction). By chromatography on a column of silica gel we isolated reticuline, isoboldine, and isocorydine from the total chloroform fraction, and glaucine, armepavine, oxyacanthine, and heliamine and the two new alkaloids intebrinine (IV) and intebrimine (V) from the total ether fraction.

All the known alkaloids that were isolated were identified on the basis of spectral characteristics and direct comparison with authentic samples. This is the first time that armepavine [2] and heliamine [3] have been obtained from a plant of the genus Berberis.

Intebrinine (IV) was isolated in the form of an oil but its hydrochloride crystallized well from methanol. The IR spectrum of the base lacked an absorption band of active hydrogen. Its UV spectrum was characteristic for the tetrahydroisoquinoline alkaloids [4]. The mass fragmentation of the hydrochloride of (I) under EI resembled that of the N-benzylisoquinoline alkaloids [5]. The presence of the maximum ion with m/z 192 and of intense ions with m/z 164 and 135 formed in cleavages a and b showed that in ring A of interbrinine there were two methoxyls and in ring D a methylenedioxy group.

The fact that (IV) was a N-benzylisoquinoline was confirmed by its PMR spectrum, which contained two two-proton singlets, at 3.60 and 3.51 ppm for the methylene protons at C-1 and C-α, respectively [5]. The nature of the signals of the five aromatic protons in the PMR spectrum of intebrinine gave grounds for stating that the methoxy groups in ring A occupied positions 6 and 7, and the methylenedioxy group in ring C positions 3' and 4'. The assignment of the chemical shifts of the protons in the PMR spectrum is given in Table 1.

Andizhan State Medical Institute. Institute of the Chemistry of Plant Substances, Uzbekistan Republic Academy of Sciences, Tashkent. Translated from Khimiya Prirodnykh Soedenii, No. 1, pp. 70-73, January-February, 1993. Original article submitted June 29, 1992.

0009-3130/93/2901-0057$12.50

TABLE 1. Details of the PMR Spectra of Intebrinine (IV) and Intebrimine (V), Taken in $CdCl_3$ (0 – HMDS; δ, ppm)

Protons	Chemical shifts; J, Hz	
	IV	V
2H-1	3,60 (2H, s)	3,62 (2H, s)
2H-3, 2H-4	2,80 (4H, m)	2,82 (4H, m)
H-5*	6,45 (1H, s)	6,49 (H, s)
OCH_3-6**	3,84 (3H, s)	3,84 (6H, s)
OCH_3-7**	3,80 (3H, s)	3,81 (6H, s)
H-8	6,58 (1H, s)	6,60 (1H, s)
2H-α	3,51 (2H, s)	3,56 (2H, s)
H-2′	6,94 (1H, d, J=1,8)	6,98 (1H, d, J=1,8)
OCH_2O (C-3′, C-4′)[a]	5,96 (2H, s)	3,84 (6H, s)**; 3,81 (6H, s)**
H-5′	6,76 (1H, d, J=8,5)	6,78 (1H, d, J=8,5)
H-6′	6,87 (1H, dd, J_o=8,5 J_m=1,8)	6,90 (1H, dd, J_o=8,5 J_m=1,8)

---

*, **The assignments of the protons may be interchanged.

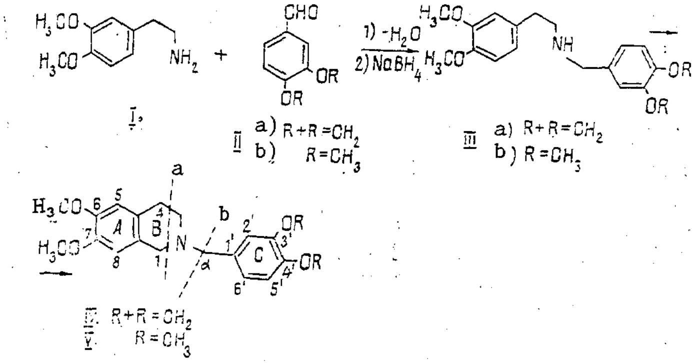
[a] In the case of (V) there are two methoxyls at C-3' and C-4'.

On the basis of the facts given, structure (IV) is proposed for intebrinine.

Intebrimine (V) was also isolated in the form of an oil and was crystallized in the form of its hydrochloride. Like (IV), from its mass and UV spectra (V) was assigned to the N-benzylisoquinoline alkaloids. The presence in the mass spectrum of (V) of intense ions with m/z 192 and 151, formed on cleavage b, indicated that there were two methoxy groups in each of rings A and C.

The multiplicities of the signals of the aromatic protons indicated that the methoxy groups occupied positions 3', 4', 6, and 7.

On the basis of its spectral characteristics, structure (V) is proposed for intebrimine.



To confirm the proposed structures, we carried out the synthesis of intebrinine (IV) and intebrimine (V) by condensing homoveratrylamine [6] with veratraldehyde (IIb) and piperonal (IIa). The amines (IIIa, b) obtained by reducing the imines with sodium tetrahydroborate were cyclized under the conditions of the Pictet–Spengler reaction to the bases (IV) and (V).

In their physicochemical constants and spectral characteristics, the compounds (IV) and (V) obtained proved to be identical with intebrinine and intebrimine, respectively.

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer, UV spectra on a Hitachi EPS-3T spectrometer (in alcohol), mass spectra on a MKh-1310 spectrometer fitted with a system for direct introduction into the ion source, and PMR spectra on a Tesla BS-567A spectrometer (Czechoslovakia) in deuterochloroform with the addition of deuteromethanol. Chemical shifts are given relative to the internal standard HMDS on the δ schale.

For TLC we used type LS 5/40 silica gel, and for column chromatography type KSK silica gel with a grain size of 125-160 μm and the following solvent systems: 1) benzene–ethanol (9:1); 2) chloroform–methanol (9:1 and 4:1); and 3) chloroform–methanol–conc. HCl (50:50:0.1).

Isolation and Separation of the Total Alkaloids from the Leaves of B. integerrima. The air-dry comminuted leaves of B. integerrima (1.6 kg) were extracted with chloroform as in [1]. This gave 3.04 g of the ether fraction and 1.44 g of the chloroform fraction of the total. The chloroform fraction (1.44 g) was separated on a column of silica gel, with elution by mixtures of chloroform and methanol in various ratios. On elution with chloroform–methanol (97:2 [sic]) 0.3 g of isoboldine was isolated, and with the (96:4) mixture of 0.4 g of isocorydine 0.5 g of reticuline.

The ether fraction was separated on a column of silica gel in the same way as the chloroform fraction. Elution with chloroform yielded 0.04 g of intebrinine (I), 0.05 g of intebrimine (II), and 0.8 g of glaucine. The (98:2) mixture gave 0.2 g of armepavine and 0.2 g of oxyacanthine; and the (96:4) mixture 0.07 g of heliamine.

The heliamine was crystallized from ether, mp 86-87°C.

IR spectrum ($\nu_{\max}^{KBr}$, cm^{-1}): 3300, 2900, 2750, 1608, 1490, 1200.

UV spectrum ($\lambda_{\max}^{C_2H_5OH}$, nm): 220 ($\log\varepsilon$ 3.7), 284 ($\log\varepsilon$ 3.6).

Mass spectrum, m/z (I, %): 193(86), 192(53), 178(6), 165(16), 164(100), 149(12), 121(14).

PMR spectrum ($CDCl_3$, δ, ppm): 2.77 (4H, s), 3.61 (2H, s), 3.20 (1H, s), 3.76 (3H, s), 3.78 (3H, s), 6.48 (1H, s), 6.55 (1H, s).

Intebrinine (IV) – an oil – was crystallized in the form of its hydrochloride, mp 223-224°C.

IR spectrum ($\nu_{\max}^{KBr}$, cm^{-1}): 2920, 2530, 1610, 1500, 1450, 1260, 1120, 1040, 940, 820.

UV spectrum ($\lambda_{\max}^{C_2H_5OH}$, nm): 206, 230 (shoulder), 287 ($\log\varepsilon$ 4.21; 3.87; 3.72).

Mass spectrum of the hydrochloride, m/z (I, %): 327 (M^+, 26), 326(23), 312(2), 206(3.5), 192(100), 176(5), 164(65), 135(82), 121(10.5).

Intebrimine (V) – an oil – was crystallized in the form of its hydrochloride, mp 169-170°C.

IR spectrum ($\nu_{\max}^{KBr}$, cm^{-1}): 2900, 2540, 1600, 1480, 1440, 1110.

UV spectrum ($\lambda_{\max}^{C_2H_5OH}$, nm): 208, 230 (shoulder), 285 ($\log\varepsilon$ 4.31; 3.84; 3.69).

Mass spectrum of the hydrochloride, m/z (I, %): 343 (M^+, 25), 342(23), 328(2), 206(3), 192(100), 176(6), 164(63), 151(81).

Synthesis of the Amines (III). A solution of 0.01 mole of homovetratrylamine in 50 ml of benzene was treated with 0.011 mole of a substitute benzaldehyde (II). The mixture was boiled under reflux for 1 h, a Dean–Stark trap being used for the azeotropic distillation of the water formed. After the benzene had been distilled off, the imine formed was dissolved in methanol and was reduced with sodium tetrahydroborate (0.015 mole) at 5°C. After evaporation, the residue was dissolved in water and extracted with chloroform. The extract was washed with water and dried with sodium sulfate. The residue after the chloroform had been distilled off was dissolved in acetone and the solution was acidified with cone, HCl to a weak acid reaction. The salt of the amine (III) that deposited was recrystallized from acetone–methanol (4:1).

N-(3,4-Methylenedioxybenzyl)-3,4-dimethoxyphenethylamine (IIIa) – hydrochloride, mp 193°C, $C_{18}H_{21}NO_4\cdot HCl$. Yield 79%.

Mass spectrum, m/z (%): 315 (M^+, 1.5), 164(44), 151(8), 135(100), 121(4).

N-(3,4-Dimethoxybenzyl)-3,4-dimethoxyphenethylamine (IIIb) – hydrochloride, mp 140°C, $C_{19}H_{25}NO_4\cdot HCl$. Yield 74%.

Mass spectrum, m/z (I, %): 331 (M^+, 1.4), 180(9), 179(9), 178(9), 152(19), 151(100).

Synthesis of (IV) and (V). A solution of 0.013 mole of the hydrochloride of an amine (III) in 50 ml of methanol was treated with 10 ml of 30% formalin and 3 drops of conc. HCl to give a strongly acid medium and then the mixture was boiled for 3 h. The methanol was distilled off, and the residue was diluted with water and made alkaline with ammonia, and the amine was exhaustively extracted with ether. The ethereal extracts were washed with water and dried with sodium sulfate. After the solvent had been distilled off, the residue was dissolved in acetone, and conc. HCl was added to pH 4. The precipitate of hydrochloride that deposited was filtered off.

Intebrinine (IV) – hydrochloride, mp 223-225°C, $C_{19}H_{21}NO_4 \cdot HCl$. Yield 76%.

Intebrimine (V) – hydrochloride, mp 171-172°C, $C_{20}H_{25}NO_4 \cdot HCl$. Yield 81%.

LITERATURE CITED

1. A. Karimov, B. Tashkhodzhaev, Ya. V. Rashkes, M. K. Makhmudov, and E. G. Mil'grom, Khim. Prir. Soedin., 65 (1993).
2. S. Yu. Yunusov, Alkaloids [in Russian], Fan, Tashkent (1981).
3. M. D. Menachery, G. L. Lavanier, M. L. Wetherly, H. Guinaudeau, and M. Shamma, J. Nat. Prod., 49, 745 (1986).
4. A. W. Sangster and K. L. Stuart, Chem. Rev., 65, 69 (1965).
5. T. Kametani and K. Ohkubo, Tetrahedron Lett., No. 48, 4317 (1965).
6. V. I. Vinogradova, M. S. Yunusov, A. V. Kuchin, G. A. Tolstikov, R. T. Sagandykov, Kh. A. Khalmuratov, and A. Alimov, Khim. Prir. Soedin., 97 (1990).

UMBROFINE AND 6-ACETYLUMBROFINE – NEW C_{18}-DITERPENE ALKALOIDS FROM Aconitum umbrosum

V. A. Tel'nov

UDC 547.944/945

Two new alkaloids – umbrofine and 6-acetylumbrofine – have been isolated from Aconitum umbrosum, and their structures have been established on the basis of spectral characteristics.

Continuing a study of the alkaloids of the roots of A. umbrosum we have isolated, in addition to the known alkaloid lycaconitine [1, 2], two new bases: umbrofine (I), $C_{23}H_{37}NO_6$, mp 110-112°C and 6-acetylumbrofine (II), $C_{25}H_{39}NO_7$, mp 174-175°C (HRMS 465.2783).

The IR spectrum of (I) showed absorption bands of hydroxy groups at 3600 and 3400-3200 cm^{-1}.

The PMR spectrum of umbrofine contained signals from the protons of the following groups: the methyl of a N-ethyl group at (ppm) 1.08 (3H, t, J = 7.5 Hz) and three methoxy groups at 3.27, 3.37, and 3.44 (s, 3H, each); and one-proton signals at 3.64 (1H, t, J = 4.5 Hz) and 4.24 (1H, s).

In the mass spectrum of (I) the maximum peak was that of the $(M - 31)^+$ ion resulting from the ejection of a methoxy group at C-1 [3]. In the ^{13}C NMR spectrum of umbrofine there were 23 signals: 3 singlets, 10 doublets, 6 triplets, and 4 quartets.

The IR spectrum of 6-acetylumbrofine contained the absorption bands of hydroxy groups at (cm^{-1}) 3554 and 3460 and of an ester carbonyl at 1730 cm^{-1}.

IN the PMR spectrum of (II) signals of the protons of the following groups were observed: the methyl of a N-ethyl group at (ppm) 0.99 (3H, J = 7.5 Hz), an acetyl group at 1.99 (3H, s), and three methoxy groups at 3.22, 3.30, and 3.38 (s, 3H each); and one-proton signals at 3.68 (1H, t, J = 4.5 Hz) and 5.13 (1H, s).

In the mass spectrum of 6-acetylumbrofine the maximum peak was, as in that of (I), that of a $(M - 31)^+$ ion.

The ^{13}C NMR spectrum of (II) contained 25 signals; 4 singlets, 10 doublets, 6 triplets, and 5 quartets.

The alkaline hydrolysis of 6-acetylumbrofine gave an aminoalcohol $C_{23}H_{37}NO_6$, mp 110-112°C, which was identified by TLC, a mixed melting point, and mass, IR, and PMR spectra as umbrofine.

Institute of Chemistry of Plant Substances, Uzbekistan Republic Academy of Sciences, Tashkent. Translated from Khimiya Prirodnykh Soedenini, No. 1, pp. 73-77, January-February, 1993. Original article submitted June 29, 1992.

0009-3130/93/2901-0060$12.50