STRUCTURE OF ILIENSINE

M. S. Yunusov, V. E. Nezhevenko, and S. Yu. Yunusov

UDC 547.944/945

We have studied the epigeal part of the plant Delphinium biternatum [1] collected in the budding–flowering stage on the slopes of the Fergana range in the Algamaidan region. Chloroform extraction yielded 1.3% of total alkaloids which were separated into ether-soluble and chloroform-soluble fractions. The chloroform-soluble fraction yielded a new alkaloid $C_{24}H_{39}NO_7$ with mp 202-203°C, which we have called iliensine [1]. The base is sparingly soluble in methanol, benzene, and acetone, and readily soluble in chloroform. Spectra and chemical characteristics of iliensine showed the developed formula $C_{19}H_{21}(N-C_2H_5)(OH)_4(OCH_3)_3$ for it. The NMR, mass, and IR spectra of iliensine are very close to those for acomonine [2]. Consequently, it may be concluded that iliensine is based on the lycoctonine skeleton. Subsequent reactions have completely confirmed this hypothesis.

Acylation of the alkaloid with acetic anhydride gave a diacetyl derivative (II). This permitted the assumption of two secondary hydroxy groups in iliensine, and this is confirmed by the NMR spectrum of (II): the signals from two geminal protons appear in the weak field.

When the alkaloid was oxidized with potassium permanganate in aqueous acetone, compound (III), $C_{22}H_{33}NO_7$, differing from the initial alkaloid by 30 mass units, was formed. Product (III) no longer contained an ethyl group and one of the secondary hydroxy groups, as follows from the acetylation of (III) with acetic anhydride, which gave a N,O-diacetyl N-nor derivative (IV). The NMR spectrum of (IV) showed the signals of the protons of two acetyl groups and no signal from a N-ethyl group. The IR spectrum of (IV) had the absorption bands of an amide carbonyl at 1630 cm^{-1} and of an ester grouping at 1730 cm^{-1}. When compound (IV) was treated with a ethanolic solution of caustic potash, the ester grouping underwent saponification, the N-acetyl group was retained (V). The facts given show that the substance formed on the oxidation of iliensine is a N-nor-anhydrohydroxy derivative, i.e., it contains an internal α-carbinolamine ether grouping. Also in harmony with this conclusion are the NMR spectra of the acetate (V) and of the diacetate (IV), which contain the signals of the $>N-CH-O-$ groupings in the form of one-proton singlets at 5.11 and 4.89 ppm, respectively, these being displaced downfield with respect to the corresponding signals in the spectrum of anhydrohydroxyacomonine by approximately 60 Hz [2], which is explained by the presence of a N-acetyl group in the case of iliensine.

Thus, it may be concluded that iliensine contains a N-ethyl group and that one of the secondary hydroxy groups is present in the immediate vicinity of the nitrogen. The secondary hydroxyl is probably located at C_3. This assumption is based on the following considerations. The mass spectrum of N-noranhydrohydroxyiliensine (III) coincides almost completely with the spectrum of anhydrohydroxyacomonine, differing only by a displacement of all the peaks by 42 m.u.

Moreover, the acetylation of iliensine gave a monoacetyl derivative (VI), as well as the diacetate. In the mass spectrum of (VI) the maximum peak is that of the $M - CH_3COO$ ion, while in the spectrum of the alkaloid itself the peaks of the $M - OH$ ion has an intensity of 36%. We have observed a similar pattern for an acomine and its acetate [2]. And, finally, the nature of the splitting of the signal of the geminal proton in the NMR spectrum of iliensine monoacetate agrees completely with that for acomonine acetate [2], which shows the location of the acetoxy group in (VI) at C_3.

On reaction with p-toluenesulfonyl chloride, iliensine forms anhydroiliensine (VII), $C_{24}H_{37}NO_6$. The NMR spectrum of (VII) shows the signals of two olefinic protons at 5.29 ppm (1 H, doublet, J = 10 Hz) and 5.82 ppm (1 H, multiplet). The chemical shifts and the nature of the splitting of the signals coincide completely with those in the spectrum of anhydroacomonine and are in good agreement with the existence of a double bond at

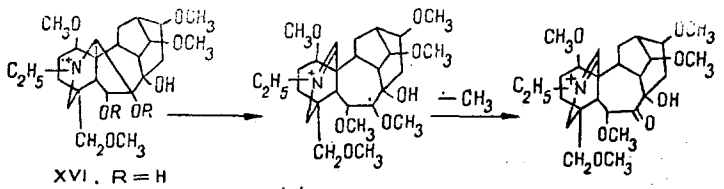
Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 770-775, November-December, 1975. Original article submitted September 29, 1974.

C_2-C_3 [2]. The fact that one of the secondary hydroxy groups is retained in anhydroiliensine is confirmed by the formation of a monoacetyl derivative (VIII). The position of the second hydroxy group at C_{10} is shown by the NMR spectra of compounds (VIII) and (IV). In these spectra, the signals from the protons geminal to the acetoxy groups are found in the form of triplets at 4.79 and 4.76 ppm (J = 5 Hz), respectively. The positions and the splitting constant of the signals are characteristic for a β-proton geminal to an acetoxy group at C_{10}.

We have previously established that a hydroxy group at C_{10} is acetylated considerably more slowly than one at C_1 [3]. The results given in the present paper (formation of the monoacetate (VI) likewise show a marked difference in the rates of acetylation of the hydroxy groups at C_3 and C_{10}.

To investigate the position of the other two hydroxy groups, deoxyiliensine (IX), obtained by the hydrogenation of anhydroiliensine, was oxidized with potassium permanganate in aqueous acetone to the 18-oxo derivative $C_{24}H_{37}NO_7$ (X). The latter was subjected to cleavage by periodic acid to the seco product $C_{24}H_{35}NO_7$ (XI). The IR spectrum of (XI) has the absorption band of a ketone in a five-membered ring at 1770 cm^{-1}, of a lactam carbonyl at 1640 cm^{-1}, and of a α,β-unsaturated ketone in a six-membered ring at 1670 cm^{-1}. The mass spectrum of (XI) is close to the spectra of the corresponding exoseco products of deoxyacomonine (XII), lycoctonine, browniine, and delphatine [2, 4]. All the alkaloids mentioned contain a diol system at C_7-C_8. The NMR spectrum of the seco product (XI) shows the signals from two methoxy groups (3.1 and 3.2 ppm, singlets, 3 H each) and from two olefinic protons at 5.95 ppm (1 H, doublet, J = 9 Hz) and 6.8 ppm (1 H, multiplet), i.e., the pattern observed for the seco-demethanol derivatives of lycoctonine alkaloids with a diol system at C_7-C_8 [4]. The facts given above show that the oxidation of oxodeoxyiliensine (X) led to the cleavage of the diol system at C_7-C_8, and a molecule of methanol was split out at the expense of the methoxy group at C_{15} [4], which led to the formation of an α,β-unsaturated ketone.

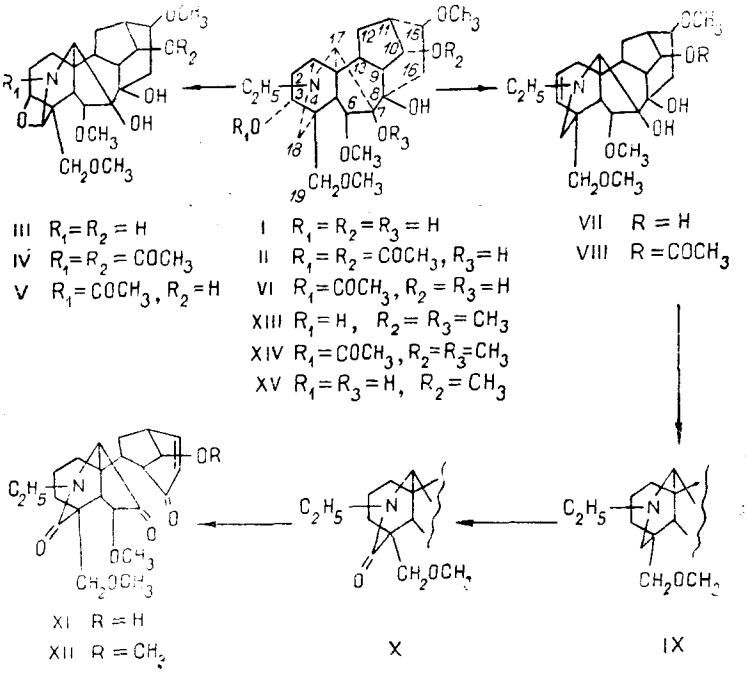
Thus, the positions found for the functional groups in iliensine are the same as in acomonine. The remaining two methoxy groups are, apparently, in view of the closeness of the properties of the alkaloids and their derivatives, at C_6 and C_{19}, as in acomonine. To confirm this, we performed a correlation of iliensine with acomonine. Both alkaloids were methylated with methyl iodide in the presence of sodium hydride. The methylation of acomonine gave a monomethyl ether (XIII) and that of iliensine gave dimethyl ether, and these compounds proved to be identical. To determine the direction of methylation, (XIII) was acetylated with acetic anhydride in pyridine, giving a monoacetate (XIV). The IR spectrum of (XIV) showed the absorption band of an ester carbonyl at 1730 cm^{-1}. In the mass spectrum, the maximum peak was that of the ion $M - CH_3COO$, and the NMR spectrum of the acetate contained the signals from one acetyl group, five methoxyls, and a proton geminal to an acetoxy group at 4.7 ppm (quadruplet, J_1 = 7 Hz, J_2 = 10 Hz). The nature of the splitting of the latter signal and its position agree with those of the proton geminal to the acetoxy group in iliensine acetate (VI). Consequently, the acetylation of the methyl ether (XIII) took place in the secondary hydroxy group at C_3, and in the case of iliensine the hydroxy group at C_{10} and one of the tertiary hydroxy groups at C_7 and C_8 were methylated. The decision between these positions was made on the basis of a study of the mass spectra of acomonine (XV), its methyl ether (XIII), demethylenedelcorine (XVI), and dimethyl demethylenedelcorine (XVII) [5]. It has been established previously that the methylation of XVI with methyl iodide in the presence of sodium hydride in dioxane solution forms (XVII) [5]. By comparing the pairs of mass spectra of (XV) and (XIII), and (XVI) and (XVII), it can be seen that in both cases on passing to the methyl ethers the intensity of the peak of the M − 15 ion in relation to the total ion current increases greatly (in the first case from 2.86 to 26.1% and in the second case form 29.8 to 49.8%). Such a sharp rise in the M − 15 peak can be explained only by the presence of a newly formed methoxy group at C_7 (see decomposition scheme), while, as is well known [6], the substituent at C_8 can be eliminated either in the form of a radical or in the form of a neutral molecule.



The results of the correlation performed permit the two remaining methoxy groups in iliensine to be located at C_6 and C_{19}. Thus, iliensine has structure I. (See Scheme on next page.)

EXPERIMENTAL

The homogeneity of the substances was checked by chromatography in a thin layer of ShSK silica gel in the benzene–methanol (4 : 1) system. The NMR spectra (deuterochloroform) were taken on a JNM-4H-100/100



III $R_1 = R_2 = H$
IV $R_1 = R_2 = COCH_3$
V $R_1 = COCH_3$, $R_2 = H$

I $R_1 = R_2 = R_3 = H$
II $R_1 = R_2 = COCH_3$, $R_3 = H$
VI $R_1 = COCH_3$, $R_2 = R_3 = H$
XIII $R_1 = H$, $R_2 = R_3 = CH_3$
XIV $R_1 = COCH_3$, $R_2 = R_3 = CH_3$
XV $R_1 = R_3 = H$, $R_2 = CH_3$

VII $R = H$
VIII $R = COCH_3$

XI $R = H$
XII $R = CH_3$

X

IX

MHz instrument with HMDS as internal standard (the values are given in the δ scale); the mass spectra on an MKh-1303 instrument fitted with a glass system for the direct introduction of the samples into the ion source; and the IR spectra (tablets with KBr) on a UR-10 instrument.

Iliensine, M^+ 453.2753; mp 203-204°C (ethanol–chloroform). NMR spectrum (ppm): 1.04 (3H, triplet, J = 7.5 Hz), 3.26 (3H, singlet), 3.31 (6H, singlet). Mass spectrum: M^+ 453 (12%), 438 (100), 436 (33), 422 (60), 420 (60). Hydrochloride mp 210°C (decomp., acetone–methanol).

O,O-Dimethyliliensine (XIII). A mixture of 75 mg of iliensine, 30 mg of sodium hydride, and 0.5 ml of methyl iodide in 15 ml of dioxane was boiled for 2 h. The precipitate was separated off and washed with chloroform, and the filtrate was evaporated. The residue was dissolved in 2% sulfuric acid and the solution was washed with ether and made alkaline with sodium carbonate, and the reaction product was extracted with ether. After the solvent had been distilled off and the residue had been crystallized from acetone, 40 mg of (III) was obtained with mp 198-202°C. Mass spectrum: M^+ 481 (26%), 466 (100), 464 (18), 450 (20), 448 (10), 434 (24), 418 (16).

O-Methylacomonine, obtained by the method given above, was identical with (XIII).

Acetyl-O-methylacomonine (XIV). A mixture of 60 mg of methylacomonine, 2 ml of acetic anhydride, and 0.25 ml of pyridine was left at room temperature for three days. After the usual working up, 40 mg of (XIV) was obtained with mp 113-117°C (hexane–ether), M^+ 523.

Monoacetyliliensine (VI). A mixture of 0.1 g of iliensine, 3 ml of acetic anhydride, and 0.5 ml of pyridine was left at 20°C for 6 h. The crude product obtained after the usual working up was chromatographed on alumina, elution being performed first with ether and then with ether–methanol (20 :1). The ether–methanol eluate yielded 60 mg of chromatographically homogeneous (VI), M^+ 495. ν_{max} 1730 cm^{-1}. NMR spectrum: 4.65 ppm (1H, quadruplet, J_1 = 7 Hz, J_2 = 10 Hz).

Diacetyliliensine (II). A mixture of 0.2 g of iliensine, 3 ml of acetic anhydride, and 0.5 ml of pyridine was left at 20°C for two days. After the usual working up, a product was obtained which was crystallized from hexane. This gave 0.12 g of (II) with mp 125-128°C. M^+ 537 (8%), 522 (20), 506 (12), 504 (12), 478 (100). ν_{max} 1735 cm^{-1}. NMR spectrum: 1.98 ppm (6H, singlet).

N-Noranhydrohydroxyiliensine (III). By the method described previously [4], 0.12 g of iliensine was oxidized with potassium permanganate in aqueous acetone. After crystallization of the product obtained from acetone, 20 mg of (III) with mp 217-220°C was obtained. M^+ 423 (2%), 408 (100), 406 (5), 392 (24), 390 (52).

N,O-Diacetyl-(III) (IV). A mixture of 40 mg of (III), 2 ml of acetic anhydride, and 0.25 ml of pyridine was left at 20°C for 4 days. After the usual working up, a chromatographically homogeneous product was obtained. M^+ 507 (0.5%), 492 (10), 478 (25), 475 (100), 460 (54), 444 (15). NMR spectrum (ppm): 2.05, 2.15 (singlets, 3H each).

N-Acetyl-(III) (V). Compound (IV) was boiled in a methanolic solution of caustic potash for 1.5 h. After the usual working up, a chromatographically homogeneous product was obtained. M^+ 465 (0.8%), 450 (4), 436 (10), 433 (100), 418 (30), 402 (18). NMR spectrum: 2.13 ppm (singlet, 3H). ν_{max} 1630 cm^{-1}.

Anhydroiliensine (VII). A solution of 0.55 g of iliensine in 10 ml of dry pyridine at 0°C was treated with 0.6 g of p-toluenesulfonyl chloride, and the mixture was left at 0°C for 17 h. The solvent was evaporated off and the residue was treated with 10 ml of 5% sulfuric acid. The acid solution was washed with ether and made alkaline with sodium carbonate, the precipitate that deposited was separated off, and the aqueous alkaline mother solution was extracted repeatedly with chloroform. The chloroform was distilled off, giving 0.2 g of (VII) with mp 136-138°C (acetone). M^+ 435 (25%), 420 (100), 402 (40). ν_{max} 3035 cm^{-1}.

O-Acetyl-(VII) (VIII). A mixture of 0.1 g of (VII), 3 ml of acetic anhydride, and 0.5 ml of pyridine was left for 2 days. The usual working up gave (VIII), which, after crystallization from hexane and recrystallization from acetone melted at 155-165°C. M^+ 477 (12%), 462 (100), 446 (10), 444 (35). ν_{max} 1735, 3055 cm^{-1}.

Deoxyiliensine (IX). Anhydroiliensine (50 mg) was hydrogenated with ethanol over platinum. The catalyst was separated off, and evaporation of the solvent yielded 45 mg of (IX) with mp 153-158°C (acetone). M^+ 437 (95%), 422 (100), 420 (7), 406 (50), 404 (65).

Oxodeoxyiliensine (X). To a solution of 60 mg of deoxyiliensine in 10 ml of acetone was added 60 mg of potassium permanganate in 40 ml of 50% aqueous acetone, and the mixture was shaken for 5 min. Then sodium sulfite was added to the reaction mixture until the purple coloration had disappeared completely. The manganese dioxide was separated off, the acetone was distilled off, the aqueous residue was acidified with 10% sulfuric acid, and the reaction product was extracted with chloroform. The chloroform was distilled off and the residue was treated with acetone. This gave 50 mg of (X), mp 105-107°C.

The Seco Product (XI). A mixture of 45 mg of (X), 50 mg of periodic acid, and 10 ml of 50% ethanol was left at 20°C for 4 days. The residue after the evaporation of the solvent was suspended in 20 ml of 2% sulfuric acid and shaken with chloroform. The chloroform was distilled off and the reaction product was crystallized from acetone. This gave 35 mg of (XI), mp 121-122°C (hexane–acetone). M^+ 417 (12%), 402 (9), 389 (100), 374 (28), 371 (29), 361 (12), 358 (13), 344 (55), 330 (26), 312 (14).

Secoexodeoxyacomonine (XII). Oxodeoxyacomonine [2] (100 mg) was added to a solution of 100 mg of periodic acid in 10 ml of water, and the mixture was left at 20°C for 4 days. The reaction product was extracted with ether. This gave 10 mg of (XII) with mp 195-197°C (ether). ν_{max} 1675, 1760 cm^{-1}. M^+ 431(8%), 403 (100), 388 (20), 385 (16), 375 (7), 372 (8), 358 (38), 343 (18), 330 (3), 326 (10), 234 (15), 211 (10), 137 (4), 101 (18), 85 (20), 83 (15).

SUMMARY

On the basis of chemical reactions and spectroscopy, it has been shown that the new alkaloid iliensine has the lycoctonine skeleton with α-hydroxy groups at C_3 and C_{10}, an α-glycol system at C_{7-8}, β-methoxy group at C_6 and C_{15}, a methoxymethyl group at C_4, and an iminoethyl group. A correlation has been made of iliensine with acomonine.

LITERATURE CITED

1. M. S. Yunusov, V. E. Nezhevenko, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 107 (1975).
2. V. E. Nezhevenko, M. S. Yunusov, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 389 (1975).
3. M. N. Sultankhodzhaev, M. S. Yunusov, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 481 (1975).
4. M. S. Yunusov and S. Yu. Yunusov, Khim. Prirodn. Soedin., 334 (1970).
5. A. S. Narzullaev, M. S. Yunusov, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 497 (1973).
6. M. S. Yunusov, Ya. V. Rashkev, and S. Yu. Yunsov, Khim. Prirodn. Soedin., 626 (1971).