DETERMINATION OF THE POSITION OF THE ACYL GROUPS AND THE NATURE OF SOME AMINO ALCOHOLS IN NATIVE ESTER ALKALOIDS OF THE GENUS VERATRUM

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The determination of the positions of the acyl groups in the ester alkaloids of Veratrum (false hellebore) presents great difficulty. As a rule, an unknown alkaloid is subjected to various transformations, e.g., complete and partial hydrolysis, esterification, oxidation of the individual alcoholic hydroxyls, and cleavage of glycol groups [1]. These operations occupy much time and are practical only if a large amount of the starting material is available. Having analyzed the structure and properties of the Veratrum alkaloids, we have noted some characteristic features which can be used in the study of the chemical structure of ester alkaloids.

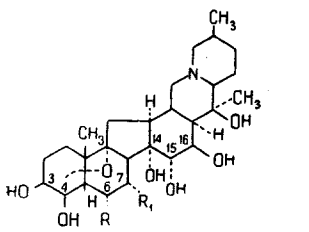
The ester alkaloids of Veratrum are based on the polyhydric amino alcohols zygadenine (I), germine (II), and protoverine (III) [1]. Mono-, di-, tri-, and tetraester alkaloids are distinguished according to their degree of esterification (Table 1).

Table 1. Ester Alkaloids of Plants of the Genus Veratrum

Alkaloid	Mp of the Alkaloid, ° C	Amino Alcohol	Acyl groups*				References
			C_3	C_6	C_7	C_{15}	
Zygacine	233—236 (ethanol)	Zygadenine	Ac			—**	[2]
Veratroylzygadenine	278—280 (absolute ethanol)	Zygadenine	Ve			—	[3]
Angeloylzygadenine	235(absolute ethanol)	Zygadenine	An			—	[4]
Germbudine	159—161 (benzene)	Germine	t-DMB		—	MB	[5, 6]
Neogermbudine	149—152 (benzene)	Germine	e-DMB		—	MB	[7]
Germidine	202—203 (ethanol)	Germine	Ac		—	MB	[8]
Germerine	203—205 (benzene)	Germine	MB		—	HMB	[6, 9, '0]
Germitrine	220—222 (petroleum ether)	Germine	MB		Ac	HMB	[10, 11]
Neogermitrine	234—235 (acetone)	Germine	Ac		Ac	MB	[11]
Germanitrine	228—229 (acetone)	Germine	An		Ac	MB	[11, 12]
Germitetrine	229—230 (benzene)	Germine	AHMB		Ac	MB	[7, 13]
Desacetylproto-veratrine A	191—192 (benzene)	Protoverine	HMB	Ac	—	MB	[14]
Desacetylproto-veratrine B	182—183 (benzene)	Protoverine	t-DMB	Ac	—	MB	[14]
Protoveratrine A	259—262 (ethanol)	Protoverine	HMB	Ac	Ac	MB	[15]
Protoveratrine B	251—255 (ethanol)	Protoverine	t-DMB	Ac	Ac	MB	[15]
Escholerine	235 (ethanol)	Protoverine	An	Ac	Ac	MB	[16]

* Ac) acetyl; Ve) veratroyl, An) angeloyl; MB) (*l*)-2-methylbutyryl; HMB) (d)-2-hydroxy-2-methylbutyryl; e-DMB) (*l*)-erythro-2,3-dihydroxy-2-methylbutyryl; t-DMB) (d)-threo-2,3-dihydroxy-2-methylbutyryl; and AHMB) erythro-3-acetoxy-2-hydroxy-2-methylbutyryl.

**Alcoholic hydroxyls not acetylated.



I $R=R_1=H$, II $R=H, R_1=OH$, III $R=R_1=OH$

We see from Table 1 that in the natural ester alkaloids of Veratrum the residues of eight acids appear as acyl

groups. They are located in the C_3, C_6, C_7, and C_{15} positions. Only acetic acid residues are found in positions C_6 and C_7, while in position C_{15} there may be a (−)-α-methylbutyric or (+)-α-hydroxy-α-methylbutyric acid residue and in position C_3 there may be a residue of any one of the acids mentioned. For these, acyl-containing monoesters are in position C_3, diesters in positions C_3 and C_{15}, triesters in positions C_3, C_7, and C_{15} (for germine) and C_3, C_6, and C_{15} (for protoverine), and tetraesters in positions C_3, C_6, C_7, and C_{15}. An exception is neogermidine (isogermidine). Its acyls are found in positions C_7 and C_{15} [17]. However, from the method of hydrolysis described by Myers et al. [6], neogermidine may form the product of partial acid hydrolysis of neogermitrine [17] and is not a native alkaloid, as is confirmed by the reactivity of the hydroxyl groups of germine. The hydroxyl group in position C_3 is more reactive than that in position C_7 [17,18]. Consequently esterification at C_7 with a free hydroxyl at C_3 is unlikely.

An interesting interrelationship has been observed between the structure of the substituent at C_7 and the melting point: alkaloids with a free hydroxyl at C_7 melt below 220° C and alkaloids in which this hydroxyl is esterified or is absent melt above 220° C. An exception is protoveratridine, the ester of germine and (−)-α-methylbutyric acid (mp 266–267° C), with a free hydroxyl at C_7. This is a product of the partial hydrolysis of germerine [9] and, apparently, like many other synthetic ester alkaloids [19] or other alkaloids subjected to the crude action of existing methods of isolation [6,9,17,20], has modifications in its fine structure. Consequently, we do not include it in the group of native alkaloids.

Table 2. Scheme for Determining the Positions of the Acyl Residues and the Nature of Some Amino Alcohols in the Ester Alkaloids of Veratrum

Number of ester groups	Mp, °C	Amino alcohols	Природа и положение ацилов**			
			C_3	C_6	C_7	C_{15}
Monoesters	>220	Zygadenine (I)	AHMB, Ac, Ve, An, MB,			—***
	<220	Germine (II)	HMB, e-DMB, t-DMB		—	—
	<220	Protoverine (III)		—	—	—
Diesters	<220	Germine (II)	Ac, Ve, An, MB, HMB,		—	
	<220	Protoverine (III)	e-DMB, t-DMB, AHMB	—	—	MB, HMB
Triesters	>220	Germine (II)	Ac, Ve, An, MB, HMB, e-DMB, t-DMB, AHMB		Ac	MB, HMB
	<220	Protoverine (III)	Ac, Ve, An, MB, HMB, e-DMB, t-DMB, AHMB	Ac	—	MB, HMB
Tetraesters	>220		Ac, Ve, An, MB, HMB, e-DMB, t-DMB, AHMB	Ac	Ac	MB, HMB

*From the solvents listed in Table 1.
**Abbreviations of the names of the acyl radicals as in Table 1.
***The alcoholic hydroxyls of the amino alcohol mentioned, which may not contain an acyl radical in this type of native ester alkaloid.

In view of the features of the structure described above and properties of the alkaloids mentioned, we have drawn up a scheme (Table 2) from which it is possible to determine the positions of the acyls in a study of the structure of the Veratrum alkaloids without having recourse to the laborious methods of partial hydrolysis, oxidation, etc., which are generally used [1,17]. It is merely necessary to determine the nature of the amino alcohol and the acyl radicals, and the number of ester groups, which can be done comparatively easily in investigating the structure of the ester alkaloids [21]. Then the data from Table 2 must be used.

For example, a diester alkaloid of germine has been isolated in hydrolysis products in which the presence of angelic and α-methylbutyric acids has been established. According to the scheme for the determination of the acyl radicals (see Table 2), an angelic acid residue in germine must occupy position 3 and an α-methylbutyric acid residue position 15.

If a di- tri-, or tetraester alkaloid simultaneously contains the acyl radicals of (−)-α-methylbutyric and (+)-α-methylbutyric acids, it is impossible to state in which position, C_3 or C_{15}, each of them is found. However, it may be stated with confidence that both positions (C_3 and C_{15}) are occupied by these acyl radicals.

The scheme that we propose permits the determination not only of the positions of the acyl radicals but, simultaneously, the form of some of the amino alcohols upon which the mono-, tri-, and tetraester alkaloids are based. For this purpose one must be guided by the following rules: monoester alkaloids with mp above 220° C contain the amino alcohol zygadenine, and triester alkaloids the amino alcohol germine; triester alkaloids with mp below 220° C, and also all tetraester alkaloids, contain the amino alcohol protoverine (see Table 2).

CONCLUSIONS

1. On the basis of literature data on the structure of the Veratrum alkaloids, a definite law for the arrangement of the acyl radicals in these ester alkaloids and an interrelationship between the melting point and the structure of the substituent in the C_7 position, and between the melting point and the types of amino alcohols upon which the ester alkaloids are based, has been found.

2. The features mentioned may be used in studying the structure of the Veratrum ester alkaloids according to a scheme which we propose.

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