PHARMACOLOGIC PROPERTIES OF CERTAIN STEROIDAL ALKALOIDS OF VARYING STRUCTURE

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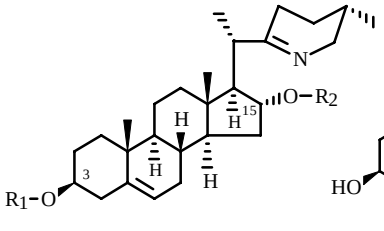
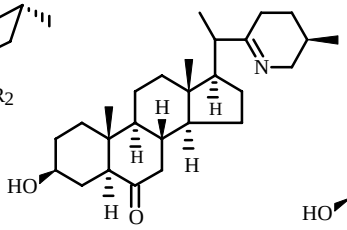
Plants of the *Veratrum*, *Petilium*, and *Korolkovia* (Liliaceae) genera contain steroidal alkaloids belonging to the normal, C-nor, and D-homosteroid types [1]. Alkaloids of these groups differ structurally. This imparts to them different pharmacological activities. Herein we present results of pharmacological research on several normal steroidal alkaloids of these plant genera that was carried out to compare differences in the pharmacological activity of the compounds as a function of the features of their chemical structure.

The alkaloids veralosinine (**1**), veralosine (**2**), and isorubiervine (**4**) were isolated from *Veratrum lobelianum*; sevkoridinine (**5**), sevkorine (**6**), and acetylsevkorine (**7**), from *Korolkovia severtzovii*; petiline (**3**), from *Petilium raddeanum* [1, 2].



1, 2

1: R_1 = H, R_2 = Ac;
2: R_1 = 3β-D-Glc, R_2 = Ac



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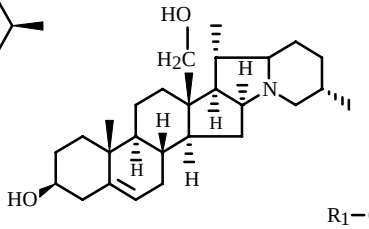

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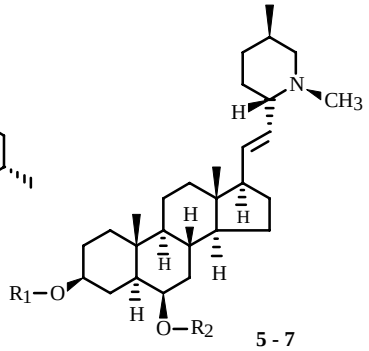

5 - 7

5: R_1 = R_2 = H;
6: R_1 = 3β-D-Glc, R_2 = H;
7: R_1 = rest acetate 3β-D-Glc, R_2 = Ac

Alkaloids **1**-**3** belong to the verasine group. Veralosine (**2**) differs from **1** by the presence of a D-glucose on C_3 and from **3**, by the presence of a carbonyl on C_6 and the lack of a double bond between C_5 and C_6.

The aminoalcohol isorubiervine (**4**) belongs to the solanidine group; sevkoridinine (**5**), sevkorine (**6**), and acetylsevkorine (**7**), to the steroidal group with a double bond between C_{20} and C_{21}.

Veralosinine (**1**), **2**, and **3** are CNS stimulators. They exhibit antagonistic effects toward sodium ethaminal and chlorhydrate and synergistic effects toward the cramping action of corazole and strychnine. They accelerate the stimulation and execution of conditioned reflexes. These compounds all are cardiotonics in both *in vitro* and *in vivo* tests. They exhibit a tendency to increase arterial pressure (AP) and antagonize the positive inotropic and chronotropic action of isadrine on isolated rat pericardium. This can be considered to be β_1-adrenolytic action. Compounds **1**-**3** possess spasmolytic action in the chloride-baric spasm model of isolated intestine. The pharmacological properties of **2** differ substantially from those of the other steroidal alkaloids by the presence of myorelaxation action. Petiline (**3**) is the only one of these alkaloids with a carbonyl on C_6. It has distinct (1/1000 of the LD_{50}) muscarinolytic action that is more evident for heart M_2-receptors, an order of magnitude greater for intestinal M_4-receptors, and two orders of magnitude less for the M_3 subtype of salivary gland receptors.

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Isorubiervine (**4**), like **1**-**3**, possesses β_1-adrenoblocking and spasmolytic action. However, in contrast with them, it is not a CNS stimulant and has no cardiotonic action. On the other hand, it decreases the force of cardiac contractions and lowers AP.

Sevkoridinine (**5**) is an aminoalcohol of a new tpye of steroidal alkaloids with a double bond between C_{20} and C_{21}. Like **1**-**3**, it stimulates the CNS. However, in contrast with them, like **4**, it decreases AP and myocardial contractions.

Sevkorine (**6**) differs from **5** by the presence of a D-glucose on C_3. It also possess spasmolytic action. The presence of the sugar removes the CNS stimulatory action that was observed for **5**. Like for **4**, the toxicity profile includes a general laxity and muscular weakness that is not connected with the myorelaxant action. In contrast with **1**-**3**, like **4**, sevkorine decreases cardiac contraction and for the first time exhibits antiarhythmic action in the aconitinic arhythmia model [4]. Acetylsevkorine (**7**) is the pentaacetyl derivative of sevkorine. Its pharmacologic properties are similar to sevkorine [6]. It differs from the other alkaloids by the presence of rather distinct vagolytic action on parasympathetic heart ganglia at doses 1/10 of the LD_{50} for muscarinolytic action.

Thus, glycosylation, acetylation, and ring closure (isorubiervine) in addition to the presence of various functional groups in the aforementioned typical steroidal alkaloids are responsible for different pharmacological properties. Spasmolytic and β_1-adrenoblocking properties are observed for all studied steroidal alkaloids. Cardiotonic action in combination with CNS stimulation is seen for verasine alkaloids **1**-**3** whereas both isorubiervine (**4**) and the sevkorine ethereal alkaloids (**6** and **7**) are not CNS stimulants and decrease myocardial contraction. Sevkorine (**6**) had antiarhythmic action. Certain pharmacological properties, for example, myorelaxant, were observed only for the ethereal glycoalkaloid veralosine (**2**). Petiline (**3**) at doses 1/1000 of the LD_{50} is a highly specific muscarinolytic agent selective for the M_2-subtype. Acetylation of sevkorine produces in **7** a distinct vagolytic action on heart parasympathetic ganglia at doses 1/10 of the LD_{50} for muscarinolytic action.

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