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Antimicrobial Activity of Veratrum Alkaloids

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Abstract—Antimicrobial activity of Veratrum alkaloids against *Pityrosporum ovale*, *Trichophyton mentagrophytes*, and *Saccharomyces cerevisiae* were investigated. Of the alkaloids tested, only jerveratrum alkaloids exhibited antimicrobial activity. The most basic structural requirement for activity of jerveratrum alkaloids is mainly due to the introduction of an oxygen in ring C regardless of the difference in structural types. Glucoside is more active than alkamine, suggesting the assistance in the transport processes.

The alkaloids obtainable from various Veratrum species, either by direct extraction or after hydrolysis, are C-27 steroidal bases and classify into two distinct chemical groups, jerveratrum alkaloids and ceveratrum alkaloids[1]. The jerveratrum unconjugated alkaloids contain only 2 or 3 atoms of oxygen and are found in hydrolyzed plant extracts in part as the free alkamines and in part in combination with one molecule of D-glucose as glucoalkaloids. The ceveratrum bases are highly hydroxylic and contain 7-9 atoms of oxygen. They usually occur esterified with various organic acids as ester alkaloids, but are in some instances unconjugated, and have never been found as glycosides.

The ceveratrum ester alkaloids possess high hypotensive activity and the relationships of the structure to activity have been reviewed by Kupchan[2]. Some of these alkaloids, for example, protoveratrine A and protoveratrine B have once been introduced into clinical use in the treatment of certain types of hypertension, but, due to the narrow range between their therapeutic and emetic doses and other side toxic effects, they have now been largely replaced by other agents that are equally or more effective, and much easier to control.[3]. On the other hand, the three jerveratrum alkaloids—jervine, cyclopamine(11-deoxojervine), and cycloposine(cyclopamine glucoside) have been shown to exhibit the teratogenic activity and their structure-activity relationships have been discussed by Keeler[4].

In our laboratory,[5] the three antimicrobial alkaloids against *Pityrosporum ovale* and *Trichophyton mentagrophytes*, have been isolated from *Veratrum grandiflorum* with the help of bioassay as a guide to fractionation at every stage and identified as jervine, its glucoside,

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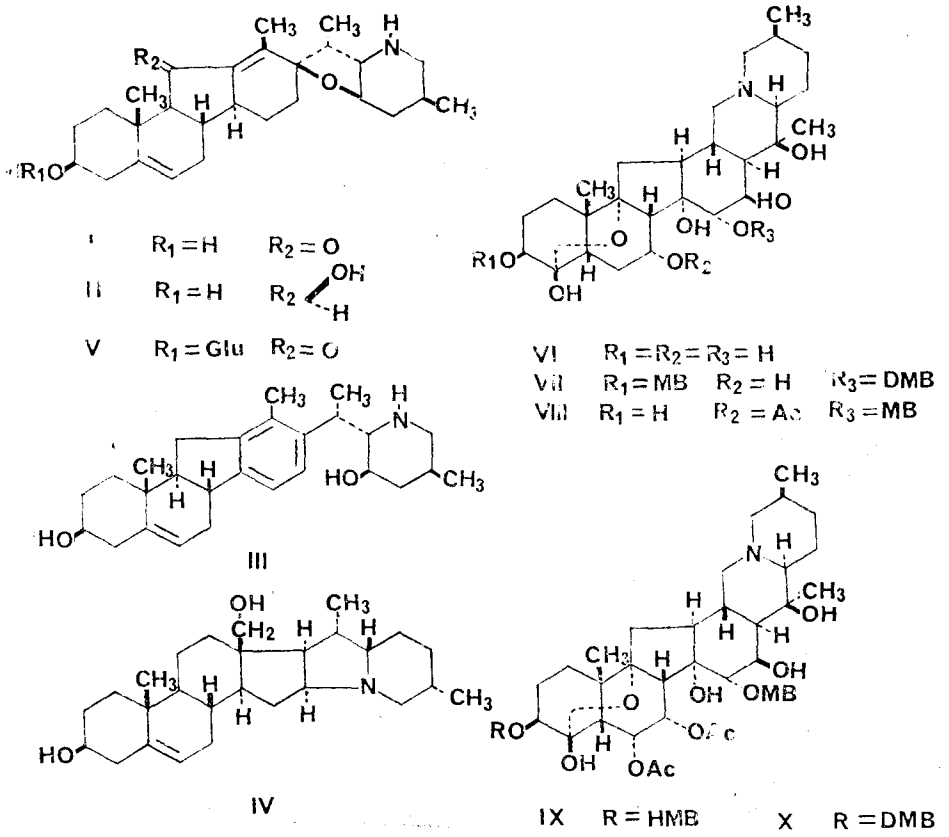

and veratramine. Recently, Wolters[6] has reported that the fungicidal action of *Veratrum album* against basidiomycetes mainly resulted by the activity of jervine.

This communication correlates the structure-activity relationships based upon the results obtained from antimicrobial assay against 3 different microorganisms. We have selected for investigation a variety of structural types including C-nor-D-homo steroid type jerveratrum alkamines; jervine(**I**), veratrobasine(**II**), and veratramine(**III**): normal steroid type; isorubijervine(**IV**): glycoside; pseudojervine(**V**): cevertrum alkamine; germine(**VI**): ester alkaloids of germine; germbudine(**VII**) and isogermidine(**VIII**): and those of protoverine; protoveratrine A(**IX**) and protoveratrine B(**X**).

The minimum inhibitory concerntrations for the antimicrobial activity obtained from the evaluation of 10 alkaloids are summaried in Table I. Jervine, pseudojervine, veratrobasine, isorubijervine, and veratramine in decreasing order were effective against *P. ovale*, pseudojervine, jervine, veratrobasine, veratramine, and isorubijervine against *T. mentagrophytes*, and pseudojervine, veratramine, jervine, veratrobasine, and isorubijervine against *S. cerevisiae*.

The results clearly suggest that jerveratrum alkaloids possess antimicrobial activity, whe-

reas ceveratrum alkaloids are devoid of activity of this type.

The compound with highest activity is pseudojervine (jervine glucoside). Veratrobasine differs structurally from jervine only in the substituent at C-11. Veratramine differs in the lack of oxygen at C-11 and oxide ring E, and presence of complete unsaturation in ring D. Isorubijervine has the normal steroidal skeleton and a hydroxyl group at C-18.

Table I—Antimicrobial action of several veratrum alkaloids.

Alkaloids	Minimum inhibitory concentration (μg/ml)		
	P. ovale	*T. menta.*	*S. cerev.*
Jervine[a]	9	72	120
Veratrobasine[b]	72	72	120
Veratramine[a]	200	72	72*
Isorubijervine[c]	72	120	200
Pseudojervine[a]	18.5	18.5	54
Germine[c]	>1000	>1000	>1000
Germbudine[d]	>1000	>1000	>1000
Isogermidine[d]	>1000	>1000	>1000
Protoveratrine A[e]	>1000	>1000	>1000
Protoveratrine B[e]	>1000	>1000	>1000

* Partical inhibition. Alkaloids were obtained from a, *V. grandiflorum*[5]; b, Sandoz; c, Squibb; d, Ayerst; and e, Nattermann.

Therefore, examination of structure-acivitty relationships in jerveratrum alkaloids reveals that (1) ring structure does not greatly affect the activity, (2) introduction of oxygen into C-11(or C-18) increases the activity, and (3) a carrier moiety such as glucose can have a profound influence on the activity by assisting in the transport processes.

EXPERIMENTAL

Veratrum Alkaloids—Jervine, pseudojervine, and veratramine were isolated from the rhizomes of *Veratrum grandiflorum* Loesner Fil. (Liliaceae) according to an extract procedure previously described.[5] The other alkaloids used in this study were all analytical samples and were obtained from laboratories as shown in Table I. The selection of these compounds was based mainly upon the availability of the samples as well as their characteristic structural types.

Antimicrobial Activity—The assay of alkaloids for their ability to inhibit the growth of *Pityrosporum ovale* (Bizz.) Cast. et Chalmers (IFO) (Littman oxgall medium), *Trichophyton mentagrophytes* (Robin) Blanchard (NI) (Sabouraud's medium), and *Saccharomyces cerevisiae* (NCYC 1200) (Wort medium) was carried out as previously described[5].

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