THE STRUCTURE OF ERVINE

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Continuing an investigation of the alkaloids of the epigeal part of Vinca erecta Rgl. et Schmalh [1], we have isolated two crystalline bases.

The first base with the composition $C_{21}H_{24}N_2O_3$ contains one methoxy group; on acetylation with acetic anhydride, an O-acetyl derivative is formed. The IR spectrum of this base has bands of the stretching vibrations of an ester carbonyl group (1720 cm^{-1}) and a double bond (1640 cm^{-1}). Oxidation of the base by a modified Kuhn-Roth method gave acetic acid, which shows the presence of a $C-CH_3$ group in it. Reduction with lithium aluminum hydride gave an amino alcohol which yielded an O, O-diacetyl derivative. The physicochemical properties of this alkaloid resemble those of akuammidine [2].

The second base with the composition $C_{21}H_{24}N_2O_3$, mp 222°–223° C, proved to be a new substance, and we have called it ervine. It contains one methoxyl and one active hydrogen. The UV spectrum of ervine has three maxima: λ_{max} 227, 282, 291 mμ (log ε 3.52, 3.77, 3.70); they are similar to those of ajmalicine. The IR spectrum of ervine has bands of the stretching vibrations of an N–H bond (3390 cm^{-1}) and bands of a $CH_3OOC-\underset{|}{C}=\underset{|}{C}-O$ grouping in the 1630 and 1710 cm^{-1} regions [3]. Saponification of the base yields an amino acid with mp 185°–190° C (decomp.), whose methylation leads to the initial ervine.

On the basis of these results and a comparison of the UV and IR spectra of ervine with the spectra of ajmalicine it has been established that ervine belongs to the alkaloids of the heteroyohimbine group, has the analytical formula $C_{19}H_{20}(=NH)(=N-)(COOCH_3)(-O)$ and is possibly a stereoisomer of ajmalicine or tetrahydroalstonine [4, 5]. Consequently, the determination of the structure of ervine reduces to elucidating the absolute configuration of the substituents C_3, C_{15}, C_{19}, and C_{20}.

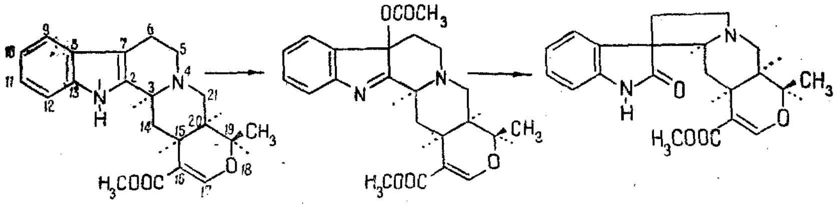
The IR spectrum of ervine has an absorption band in the 2750 cm^{-1} region indicating the α-orientation of the substituent at C_3 and the translinkage of the C/D rings. If it is considered that the substituent at C_{15} in heteroyohimbine alkaloids has the α-orientation, only the configuration of the substituents at C_{19} and C_{20} remains uncertain.

It is known that the alkaloids of this series containing a trans-C/D and a cis-D/E linkage of the rings form a methiodide with difficulty because of hindrance to the approach of methyl iodide to the nitrogen atom (b) [5]. The formation of a methiodide from ervine also requires prolonged heating. The base apparently has the cis-D/E linkage of the rings, i.e., the substituent at C_{20} has the α-orientation.

To confirm this, ervine (II) was oxidized with lead tetraacetate to give acetoxyervine (III); the IR spectrum of (III) lacked the band of a N–H bond and had a band of the absorption of the $OCOCH_3$ group (1755 cm^{-1}). The isomerization of acetoxyervine in dilute acetic acid led to hydroxyindole-ervine (IV).

The nature of the UV and IR absorption curves of (IV) show that the base is a hydroxyindole derivative. The properties of this base differ from the properties of the known hydroxyindole alkaloids. It has been established that the hydroxyindole bases are produced from the indole analogs under the action of lead tetraacetate only when the D/E rings have a cis-linkage [6]. The production of hydroxyindole-ervine confirms that the D/E rings in ervine have the cis linkage.

On the basis of these results structure (II) with the 3α, 15α, 19α, and 20α configurations of heteroyohimbine is proposed for ervine; it differs from tetrahydroalstonine [5] by the configuration of the carboxymethyl at C_{19}.



II III IV

Experimental

Akuammidine. This substance crystallized from methanol with mp 242°–243° C, $[\alpha]_D$ +26.9°, (c 2.1; methanol). UV spectrum (in alcohol): λ_{max} 227, 281 mμ (log ε 4.54, 3.93).

Found, %: C 71.40, 71.50; H 7.26, 7.04; N 8.02, 8.11; OCH_3 7.90, 7.50; H_{act} 0.64, 0.64; mol. wt. 342 (mass spectrometry). Calculated for $C_{21}H_{24}O_3N_2$, %: C 71.56; H 6.86; N 7.96; OCH_3 8.79; $2H_{act}$ 0.57; mol. wt. 352.4.

O-Acetylakuammidine. The base was heated with acetic anhydride in a water bath for 3 hr. A substance with mp 253°–254° C (decomp., from methanol) was isolated. UV spectrum (in alcohol): λ_{max} 227, 283 mμ (log ε 4.50, 3.90).

Found: C 69.16, 69.40; H 6.58, 6.82; N 6.83, 6.75. Calculated for $C_{23}H_{26}O_4N_2$ %: C 70.01; H 6.65; N 7.11.

Akuammidinol. This was obtained by reduction of an ethereal solution of the base with an excess of lithium aluminum hydride, mp 258°–280° C (decomp. from ether).

Found, %: N 8.57, 8.44. Calculated for $C_{20}H_{22}O_2N_2$, %: N 8.63.

O,O-Diacetylakuammidinol. This separated when akuammidinol was heated for 5 hr with acetic anhydride in a water bath, mp 255°–256° C [decomp., from a mixture of ethyl acetate and petroleum ether (1:1)]. UV spectrum: 226, 280 mμ (log ε 4.45, 3.80).

Ervine. Crystallized from methanol with mp 222°–223° C; $[\alpha]_D$ −57.3° (c 2.01; methanol); −83.5° (c 0.3; pyridine). UV spectrum: λ_{max} 227, 282, 291 mμ (log ε 3.52, 3.77, 3.70).

Found, %: C 71.90, 71.50; H 6.90, 6.80; N 7.71, 7.76; OCH_3 5.64, 5.62; H_{act} 0.31, 0.29. Calculated for $C_{21}H_{24}O_3N_2$, %: C 71.56; H 6.86; N 7.96; OCH_3 8.73; H_{act} 0.28.

Ervine gave a crystalline hydriodide with mp 255°–258° C (decomp.), a hydrochloride with 265°–268° C (decomp.), and a hydrobromide with mp 285°–286° C (decomp.).

Ervine methiodide. This was formed when the base was heated with methyl iodide in a water bath for 6 hr, mp 258°–260° C (decomp., methanol).

Ervinic acid. A mixture of 0.2 g of the base and 10 ml of 5% methanolic caustic potash was boiled for 3 hr. An amino acid (0.15 g) with mp 185°–190° C (decomp.) was isolated from the saponification product.

When an ethereal solution of diazomethane was added to an ethereal solution of the amino acid ervine was reformed (after two days).

Acetoxyervine. A solution of 0.80 g of lead tetraacetate in 10 ml of methylene chloride was added to a solution of 0.5 g of ervine in 5 ml of methylene chloride and the mixture was shaken at room temperature for 10 min. The precipitate of lead diacetate that deposited was separated off and washed three times with 5 ml portions of methylene chloride, and the combined methylene chloride solution was chromatographed on alumina. Elution was carried out with methylene chloride.

Fractions 1–5 yielded 0.3 g of crystals of acetoxyervine with mp 188°–190° C, $[\alpha]_D$ +87.14° (c 0.7; methanol).

Hydroxyindole-ervine. A solution of 0.2 g of acetoxyervine in 20 ml of methanol was treated with 1.5 ml of water and one drop of glacial acetic acid. The mixture was heated in a water bath for 90 min. Then the solvent was distilled off in vacuum to dryness and the residue was dissolved in water; the resulting solution was made alkaline with a solution of sodium carbonate and was extracted with ether. The residue from the evaporation of the ether (0.18 g) was dissolved in 5 ml of benzene and chromatographed on alumina. On elution with ether, fractions 3–5 gave hydroxyindole-ervine with mp 196°–200° C. UV spectrum: λ_{max} 246, 282 (log ε 4.14, 3.16).

Summary

Akuammidine and a new base ervine have been isolated from the epigeal part of *Vinca erecta* Rgl. et Schmalh. Ervine is an isomer of tetrahydroalstonine and differs from it by the configuration of the carboxymethyl group at C_{19}.

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