

ISOLATION OF RHAZIDINE AND AKUAMMIDINE FROM ASPIDOSPERMA  
QUEBRACHO BLANCO. THE STRUCTURE OF RHAZIDINE.

S. Markey and K. Biemann

Department of Chemistry, Massachusetts Institute of Technology,  
Cambridge, Massachusetts

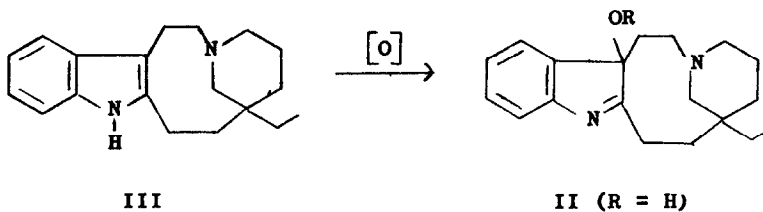
B. Witkop

National Institute of Arthritis and Metabolic Diseases,  
National Institutes of Health, Bethesda, Maryland

(Received 8 November 1966)

During a reinvestigation of the alkaloids of the bark of Aspidosperma quebracho blanco<sup>1</sup>, two major alkaloids previously unreported in this plant were isolated. In an effort to investigate the polar and thermally less stable components, thin layer chromatography rather than gas chromatography was used and led to the isolation of akuammidine (I) and rhazidine (10% and 5% of the total crude bases, respectively), identified by melting points, ultraviolet and mass spectra. The structure of akuammidine (I) had been established previously<sup>2</sup>, but not that of rhazidine, isolated from Rhazya stricta<sup>3</sup> and Gonioma kamassi<sup>4</sup>.

It had been proposed<sup>5</sup> that rhazidine is related to rhazidigenine (II) by addition to the  $\beta$ -hydroxy group of some sensitive polyhydroxy function R, which might be undetectable by mass spectrometry, the technique primarily used in that work. Rhazidigenine (II) can be obtained from rhazidine by "acid hydrolysis"<sup>5</sup>, and was shown to be identical with a product resulting from the peracid oxidation of quebrachamine (III)<sup>6</sup>.

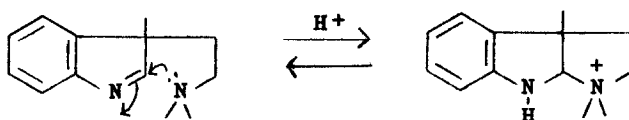


Rhazidigenine (II, m.p. 187<sup>o</sup>) and rhazidine (m.p. 285<sup>o</sup> dec.) have the same mass spectra and ultraviolet spectra (in ethanol), but differ widely in volatility and solubility as well as infrared and nuclear magnetic resonance spectra and optical rotation.

At the time this oxidation product of quebrachamine was characterized, it was noted<sup>6</sup> that:

- (1) the ultraviolet spectrum is characteristic of a dihydroindole rather than a  $\beta$ -hydroxyindolenine
- (2) there is an apparent Beer's Law deviation in the change of ultraviolet absorbance with concentration
- (3) there is a marked hysteresis upon back titration during pK measurements.

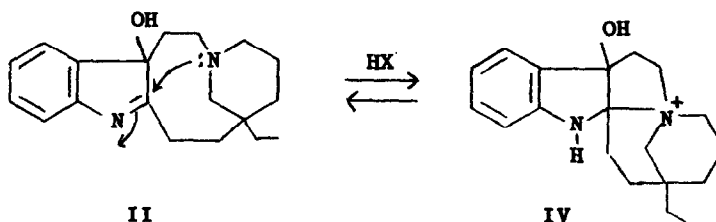
It was suggested that II undergoes tautomerization of the type shown below.



From some of our work (e.g. different work-up of the "hydrolysis", n.m.r. spectra, etc.) on the structure of rhazidine which was carried out before Spiteller's paper<sup>5</sup> appeared, it was doubtful that rhazidine could contain a polyhydroxy substituent.

The nature of rhazidine became apparent upon repeating the oxidation of III as previously described<sup>6</sup>, but washing the ether phase with sodium chloride solution. This variation produced the hydrochloride of II which proved to be identical with rhazidine as judged by mixture melting point, mass, infrared and ultraviolet spectra, optical ro-

tation, and elemental analysis. The tautomerization originally proposed<sup>6</sup> accounts for the differences between "rhazidigenine" (II) and rhazidine, which would therefore be IV.



This assignment is supported by the ultraviolet spectrum of II in heptane ( $\lambda_{\max}$  210, 281, 292, 307  $\mu$ ;  $\log \epsilon$  4.33, 3.66, 3.62, 3.58) which is that of a  $\beta$ -hydroxy-indolenine and is similar to the ultraviolet spectrum of rhazidine in ethanol with strong base ( $\lambda_{\max}$  220, 283, 293, 307  $\mu$ ;  $\log \epsilon$  4.28, 3.69, 3.70, 3.68). Rhazidine in neutral ethanol shows absorption at  $\lambda_{\max}$  236, 293  $\mu$ ;  $\log \epsilon$  3.91, 3.38. Furthermore, there is no shift upon addition of acid to an alcoholic solution of II or IV, a behavior characteristic of the Ar-N-C-N<sup>+</sup> system<sup>7,8</sup>. The dramatic dependence on pH of the optical rotation of rhazidine confirms these conclusions. In neutral or acidic ethanol, a low rotation is observed ( $\alpha_D$   $-37^\circ$ ). However, upon stepwise addition of strong base, the rotation approaches  $-612^\circ$ , returning to  $-40^\circ$  when re-acidified.

Thus, the "rhazidine" of the literature is the quaternary hydrochloride (IV) of II. In analogy to echitamine<sup>9</sup>, the name "rhazidigenine" should therefore be replaced by "rhazidine base" which is correctly represented by structure II, while IV ("rhazidine") represents "rhazidine salt". Thus it becomes impossible as well as irrelevant to decide which form is present in the plant and therefore represents the native alkaloid.

The isolation of rhazidine has paralleled the isolation of quebrachamine in plant extracts, thus raising the question whether rhazidine is an artifact of air oxidation of the extract. However, since rhazidine is a major alkaloid in A. quebracho, the apparent lack of its decomposition products (oxindoles and indoxyls) which are readily formed during air oxidation of quebrachamine, seem to preclude this possibility.

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Acknowledgment:

This work was supported by research grants from the National Aeronautics and Space Administration (NsG 211-62) and the National Institutes of Health (GM 09352).