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IONIZATION EQUILIBRIA OF RAUWOLFIA ALKALOIDS IN CONCENTRATED HYDROXIDE SOLUTIONS

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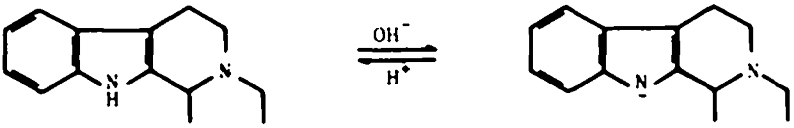
Abstract.- The ionization equilibria at 25ºC in aqueous potassium hydroxide solutions of several Rauwolfia alkaloids and 2,3-dimethylindole as model compound have been investigated by U.V. spectrophotometry. Plots of the logarithms of the ionization ratios against the H- acidity function gave straight lines whose slopes are very close to unity. The pK_{BH} values thus obtained are reported.

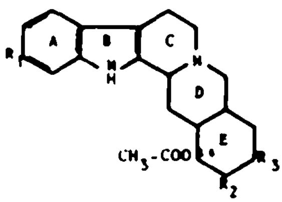
We have recently studied the protonation equilibria in sulfuric acid solutions of several Rauwolfia alkaloids[1]. These indole alkaloids obey the H_I acidity function established by Hinman and Lang for indole ring protonation[2], which suggest that these compounds, as typical indoles, behave as carbon bases.[3]

Since indoles are also acidic compounds[4,5] because of the dissociation of the -NH- proton, it should be expected that the presence of the indole ring on Rauwolfia alkaloids gives these compounds weakly acidic properties. Therefore, in continuation of our work on the protonation of Rauwolfia alkaloids we have now examined their ionization equilibria in concentrated hydroxide solutions, in an attempt to complete the prototropic characterization of these compounds.



Scheme 1.- Ionization equilibria of Rauwolfia alkaloids in concentrated hydroxide solutions.

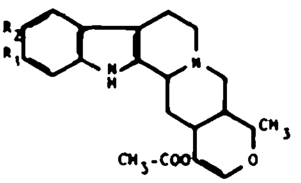
We have selected the following alkaloids; yohimbine (I) and its isomer corynanthine (II), reserpine (III) and reserpiline (IV) in order to study the influence of their structural differences on acidity. We have also included 2,3-dimethylindole as model compound. It is to be noted that, to our knowledge, no work appears to have been carried out on the study of such acid-base behaviour of these alkaloids.



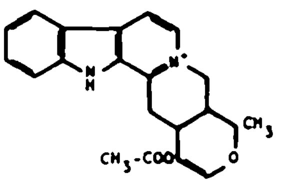
I.- Yohimbine
$R_1=R_3=H$; $R_2=OH$; C-16α

II.- Corynanthine
$R_1=R_3=H$; $R_2=OH$; C-16β

III.- Reserpine
$R_1=R_2=CH_3O$; $R_3=3,4,5(OCH_3)C_6H_2-COO$



IV.- Reserpiline
$R_1=R_2=CH_3O$



V.- Serpentine

EXPERIMENTAL

Alkaloids were the kind gift of Boehringer and Sohn, and 2,3-dimethylindole was purchased from EGA-chemie. All these materials were of the best available quality and were used without further purification. Stock solutions were prepared in methanol. The aqueous hydroxide solutions were prepared from potassium hydroxide Merck R.A. as described by Yagil[4] and were standardized against standard sulfuric acid solutions.

The spectrophotometric method used to determine the acidities was basically the same as that employed previously[1]. UV-spectra and absorbance measurements were made on a Lambda-V spectrophotometer whose cell compartment was thermostatted at 25.0±0.1 ºC. The necessary solutions for absorption measurements (c.a. $5x10^{-4}$ M) were prepared by pipetting aliquots of the indicator solutions, in amount sufficient to give accurately measurable absorbances , into hydroxide solutions. Since the hydroxide solutions appreciably absorb at the wavelengths used for absorption measurements, hydroxide solutions of the same concentrations to the test solutions were used as references. These solutions were usually stable although warming in hot water was necessary to bring about complete dissolution. Only reserpiline solutions were unstable and because of the above complication, difficulty was encountered in obtaining realiable data by zero time extrapolation. Therefore, results obtained with this alkaloid should be regarded only as an estimation.

RESULTS AND DISCUSSION

In Figure 1 are shown spectra from 240 nm to 360 nm of yohimbine in 0.1 M KOH (acid form) and 14 M KOH (basic form). These are typical of the spectra obtained from the acid and basic forms of the other alkaloids and 2,3-dimethylindole. The absorption peak of the acid form at 280 nm shifts to 285-290 nm upon conversion to base. Moreover, an additional shoulder appears at 310-320 nm which is specially suited to ionization ratio determinations since the acid form practically does not absorb at these wavelengths.

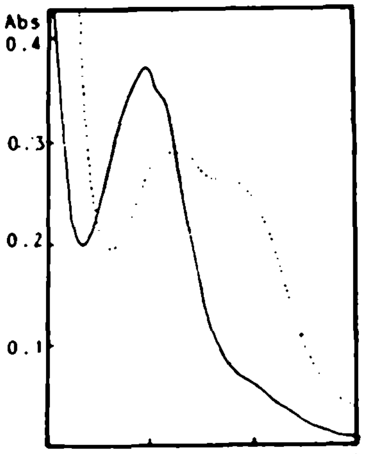


Figure 1.- Absorption spectra of yohimbine in 0.1 M KOH (—) and 14 M KOH (---).

The ionization ratios, I, were determined by usual procedure[6] from absorbance measurements of the free acid, the conjugate base and some mixtures of both forms. In obtaining these data we have been careful to use points corresponding to log I values within ±0.75 because clear deviations from parallel behaviour were observed beyond these limits.

Plots of log I against the H- acidity function defined by Yagil[4] gave straight lines whose correlation coefficients and slopes are given in Table 1. It can be noted that the values of the slopes were sufficiently close to unity to conclude that the ionization of the studied compounds follow the H- acidity function. Hence, the pK_{BH} values were calculated using the equation (1) and the data are listed in Table 1. We have also included in this Table pK_{BH} values for other related compounds previously determined.

$$pK_{BH} = H- + \log I \qquad (1)$$

As can be seen from data in Table 1, yohimbine, corynanthine, reserpine, and reserpiline have very similar pK_{BH} values in spite of their structural differences. Moreover, the pK_{BH} of these alkaloids are comparable with that of the parent compound 2,3-dimethylindole. Apparently, this much variation in ring size neither affects the acidity.

It is interesting to note that this is not the situation for the protonation equilibria,[1] where the acidity range for the same compounds cover more than 7 pK_a units on the H_I acidity function. It is consistent with the different effects of both equilibria on the indole ring aromaticity. Thus, whereas the indole ring protonation disrupts the aromaticity and, therefore, it should be expected to be more prone to structural effects, the -NH- proton can be removed without disruption of the indole aromaticity.

TABLE 1: Ionization data for Rauwolfia alkaloids and related compounds measured in KOH at 25ºC.

Compound	λ(nm)[(a)]	d(logI)/d(H-)[(b)]	r[(c)]	pK_{BH}
2,3-dimethylindole	310	-1.10±0.1	0.996(8)	15.43±0.05
Yohimbine	312	-1.06±0.1	0.996(7)	16.09±0.04
Corynanthine	312	-1.07±0.1	0.992(6)	15.93±0.06
Reserpine (d)	298	----	---	15.5 ±0.5
Reserpiline	325	-1.19±0.27	0.987(6)	15.3 ±0.3
Serpentine (f)	---	----	---	11.51±0.05
Harman (g)	---	----	---	14.6 ±0.1

(a) Wavelength employed for measurement, but not λ(max). (b) I.e. the slopes of plots of log I vs H-. (c) Correlation coefficients of these plots. The figures in parenthesis are the number of points taken. (d) pK_a value is only an estimation. (f) Ref. 7. (g) Ref. 8.

In this latter equilibrium only those structural variations which stabilize preferentially the indolate ion, by accepting part of the negative charge, might be expected to have marked influence on acidity. It is not the case of the methoxy substituents, which do not provide additional resonative forms to stabilize the anion.

Resonance stabilitation may produce much larger changes in acidity, as it is illustrated by harman (1-methyl-3H-pyrido-[3,4-b]indole or 1-methyl-β-carboline) and serpentine (V) which are about 1 and 4 pK units more acid than 2,3-dimethylindole, respectively. The presence of the fully aromatic β-carboline ring in these compounds extends the conjugation and consequently the stabilization of the indolate anion by delocalization of its charge. Moreover, the positively charged quaternary nitrogen atom in serpentine is an additional factor for the anion stabilization.

As a result of this effect, serpentine is a stronger acid than harman.

ACKNOWLEDGMENT

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