951. *A Comparative Study of Hydrolysis Rates of Some Indole Alkaloids.*

By M. J. Allen.

Hydrolysis rates of some indole alkaloids have been correlated with structure. The most prominent effect was when the hydroxyl group in many of these bases effectively formed hydrogen bonds with the carbonyl of the methoxycarbonyl group.

As the stereochemical structures of many indole alkaloids are known,[1] it is possible now to correlate these with their hydrolysis rates. For this purpose the hydroxy-esters corynanthine, methyl deserpidate, methyl isoreserpate, methyl *N*-methylreserpate, α-yohimbine, 3-epi-α-yohimbine, and yohimbine were chosen.

Experimental.—The alkaloids used were analytically pure. The 1,4-dioxan (spectrophotometric grade, Matheson Coleman and Bell) did not require further purification before use as it was found to be free from peroxide. A 0·02M-sodium hydroxide solution was prepared in 50% aqueous dioxan.

Before each experiment the alkaloids were dissolved in the dioxan so as to yield approximately a 0·01M-solution except in the case of methyl isoreserpate and methyl *N*-methylreserpate where, owing to limited supply, about half this concentration was used. The experiment was performed by pipetting 1 ml. each of the alkaloid and the sodium hydroxide solutions into 10 ml. glass-stoppered flasks; these were placed in a constant-temperature bath kept at 40° ± 5°. Results were duplicated at 5 or 6 timed intervals. At each interval two flasks were removed and quenched in an ice-bath, and the solutions titrated potentiometrically with 0·01N-hydrochloric acid, a microburette readable to 0·0005 ml. being used. The first flasks removed from the bath were used as the zero time in the calculations of this second-order reaction according to the equation

$$k = [2{\cdot}303/t(a - b)] \log [b(a - x)/a(b - x)]$$

where a and b are the concentrations (in moles/l.) of the sodium hydroxide and the alkaloid, and t is the time (in minutes).

Results.—

Alkaloid	k	Alkaloid	k
Yohimbine (I)	1·29 ± 0·04	3-Epi-α-yohimbine (IV)	4·07 ± 0·03
Corynanthine (II)	0·130 ± 0·002	Me reserpate (VI; R = OMe, R′ = H)	1·39 ± 0·05
α-Yohimbine (III)	3·83 ± 0·12	Me deserpidate (VI; R = R′ = H)	1·38 ± 0·02
Me isoreserpate (V)	0·0697 ± 0·0002	Me *N*-methylreserpate (VI; R = OMe, R′ = Me)	4·98 ± 0·13

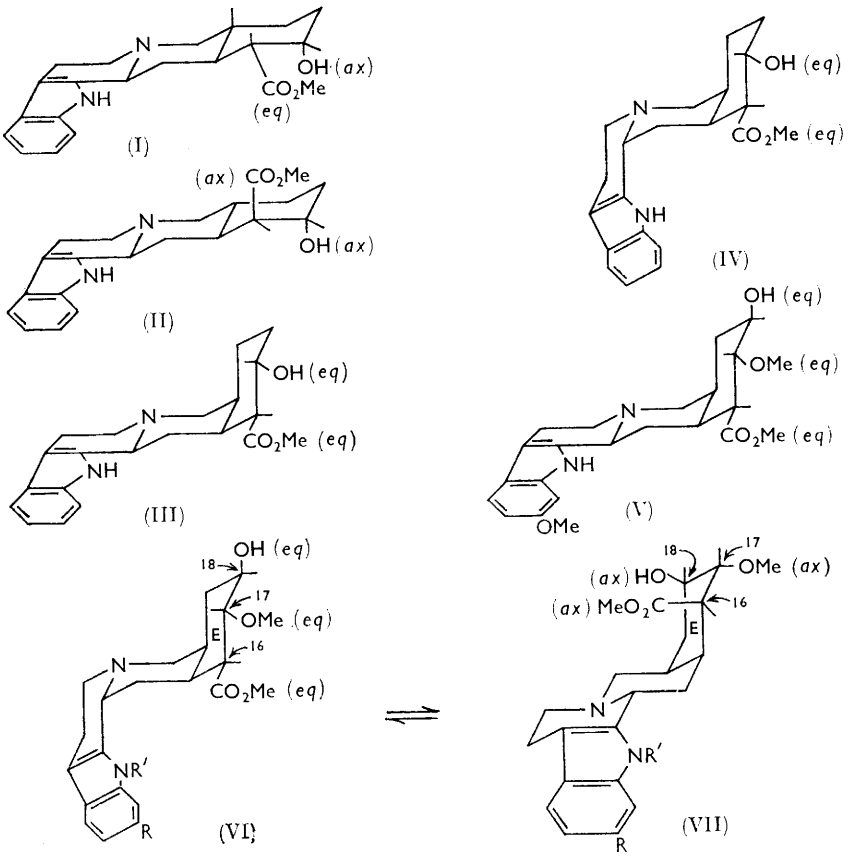
Discussion

The alkaloids investigated fall essentially into two major stereochemical catagories: the *trans*-locked D–E ring system, of which yohimbine and corynanthine are members, and the other alkaloids studied which belong to the *cis*-locked D–E ring system. Any attempt to correlate one system with the other based on the data on hand would be conjectural. However, some correlation can be made between the hydrolysis rate constant and stereochemical structure within each system.

A comparison of yohimbine (I) (k = 1·29) and corynanthine (II) (k = 0·13) shows one significant stereochemical difference. In yohimbine the hydroxyl group is axial while the methoxycarbonyl group is equatorial. The close proximity of these two facilitates hydrogen bonding which apparently enhances hydrolysis. The hydroxyl and the methoxycarbonyl group in corynanthine are both in axial positions, which diminishes the possibility of their forming a hydrogen bond. In addition, in this instance there is also steric compression on the axial methoxycarbonyl group which may interfere with the hydrolysis.

[1] Woodson, Youngken, Schlittler, and Schneider, "*Rauwolfia*," Little, Brown and Co., Boston, 1957.

Therefore the slower rate for corynanthine might very well be attributed to the two factors in effect simultaneously.



In the *cis*-locked D–E ring series the situation is somewhat more complex. Here, there is the possibility of two conformational isomers' existing in equilibrium in the original solution. In one, all the substituents on ring E are equatorial, and in the other all are axial. The rate of hydrolysis would therefore then depend on (*a*) the concentration of the two conformational isomers in solution, (*b*) the speed at which one form will be converted into the other, and (*c*) the rate of attack by hydroxyl ion on each of the two forms.

In methyl isoreserpate (V) (k = 0·0697) the preferred form is probably, as shown, that in which all substituents on ring E are equatorial. If they were axial, a considerably faster hydrolysis would be expected as in methyl reserpate (VI; R = OMe, R′ = H) (see below) because of the then closer proximity of the hydroxyl to the methoxycarbonyl group (1,3-interaction). If the substituents in ring E were axial, the indole moiety would also have to be axial with respect to ring C, resulting in a very strained conformation which probably does not exist to any great extent.

The argument used for the suggestion of the all-equatorial configuration for methyl isoreserpate (V) may also be applied to α-yohimbine (III). Here the predominant equatorial isomer would be expected to be hydrolysed faster because of the closer proximity of the hydroxyl to the methoxycarbonyl substituent (1,2-interaction).

As 3-epi-α-yohimbine (IV) (k = 4·07) has essentially the same reaction rate constant as α-yohimbine, one is tempted to suspect that that conformational isomer predominates

in which all substituents on ring E are equatorial. In the particular case of 3-epi-α-yohimbine the closer proximity of the indole-nitrogen atom to the ester group in no way appears to affect its hydrolysis rate as compared with that of α-yohimbine.

The fact that methyl reserpate (VI; R = OMe, R′ = H) (k = 1·39) and methyl deserpidate (VI; R = R′ = H) (k = 1·38) undergo hydrolysis so much faster than methyl isoreserpate (V) indicates that the preferred conformation (VI) in which the hydroxyl, methoxyl, and methoxycarbonyl groups are all equatorial [2] is not the predominant form undergoing hydrolysis, but it is that conformation (VII) in which these substituents are axial that is being hydrolysed preferentially. Here a 1,3-diaxial interaction between the 18-hydroxyl and the 16-methoxycarbonyl group assists hydrolysis.

Although it appeared in the comparison of α-yohimbine and 3-epi-α-yohimbine that the closer proximity of the indole-nitrogen atom to the ester group in the latter compound exerted no noticeable effect on the hydrolysis rate constant, it did appear to influence the rate of hydrolysis of methyl reserpate. Thus, when the hydrogen on the indole-nitrogen atom was replaced by a methyl group [3] the hydrolysis rate increased to 4·98. One possible explanation for this is that in these instances where two conformational isomers may exist, that in which there is greatest interaction between the indole NH and the methoxycarbonyl group will be the predominant isomer owing possibly to its being essentially locked in this position by a hydrogen-bond. When this "bridge" was eliminated, as in methyl *N*-methylreserpate (VI; R = OMe, R′ = Me), it was possible for more of that isomer to be formed in which all substituents of ring E were axial: hence the higher hydrolysis rate constant. The reason why an effect was not observed in comparing 3-epi-α-yohimbine with α-yohimbine can be explained on the basis that in the former compound the "bridge" maintained the predominant configuration which was ideally suited for an internally assisted hydrolysis.

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[2] Aldrich *et al.*, *J. Amer. Chem. Soc.*, 1959, **81**, 2481.
[3] Huebner, *J. Amer. Chem. Soc.*, 1954, **76**, 5792.