excited state of I. We expect that a study on the proton dissociation of the corresponding trisulfoxides and trisulfonium compounds will shed further light on the nature of the unusual reactivity of this bicyclic compound.

TABLE II

ULTRAVIOLET SPECTRA OF SULFIDES IN DIOXANE[a]

Compound	λ_{max}, mμ	log ε
I	248	3.1
II	236	3.0
III	236	2.8

[a] These spectra were the same in ethanol solution containing 0.1 *M* of sodium ethoxide.

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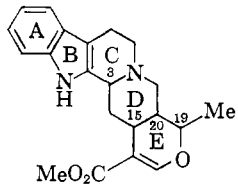
THE STEREOCHEMISTRY OF AJMALICINE AND TETRAHYDROALSTONINE[1]

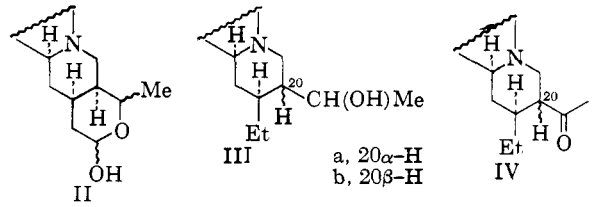
Sir:

While the relative configuration of C(3)-H and C(15)-H in the alkaloids (I) ajmalicine and tetrahydroalstonine has been shown to be *cis*[2] and their absolute configuration in ajmalicine to be α,[3] the stereochemistry of C(19) of neither alkaloid is known and that of C(20) is based on non-classical, as yet untested, investigations.[2,4] We now wish to report data from degradation and proton magnetic resonance studies which revise previous structure assignments and establish the complete stereochemistry of ajmalicine and related alkaloids.



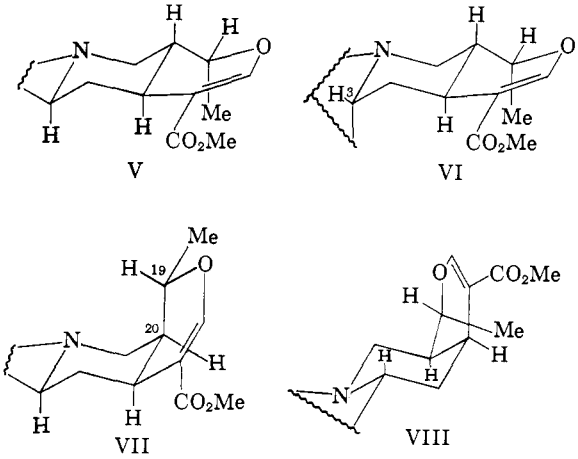
I

Alcoholic alkali and short aqueous acid treatments[3] of tetrahydroalstonine (I) yielded tetrahydroalstonial (II), m.p. 173–177°, 210–214° (Found: N, 8.83)[5] which on Wolff–Kishner reduction afforded 19-corynantheidol (IIIa); picrate, m.p. 216–222° (Found: C, 57.07; H, 5.62; N, 13.63). Oppenauer oxidation of the latter gave 19-corynantheidone (IVa), m.p. 152–153° (Found: C, 77.17; H, 8.27; N, 9.41), which was converted to 18,19-dihydro-19-corynantheone (IVb)[3], m.p., m.m.p. 225–228°, on sodium methoxide treatment. Sodium borohydride reduction of IVb yielded ajmaliciol (IIIb),[3] m.p., m.m.p. 198–200°, and 19-isoajmaliciol, m.p. 195–197° (Found: C, 76.02; H, 8.82; N, 9.16). These facts prove ajmalicine to be a D/E *trans* and tetrahydroalstonine a D/E *cis* system. Furthermore, the latter represents one more alkaloid belonging to the biosynthetically related α C(15)-H indole alkaloid family.[3]



II III a, 20α-H b, 20β-H IV

Raney nickel-induced hydrogenation of 3,4,5,6-tetradehydroakuammigine[2] to tetrahydroalstonine at high pH confirmed the previous claim[2] that akuammigine is 3-isotetrahydroalstonine. Hence the four possible stereochemical forms of the backbone of ring E heterocyclic indole alkaloids are now represented as: *normal*-ajmalicine (V); *pseudo*-3-isoajmalicine (VI)[2]; *allo*-tetrahydroalstonine (VII) and *epiallo*-akuammigine (VIII). These structural assignments are corroborated by p.m.r. spectral findings. 3-Isoajmalicine (VI), the only equatorial C(3)-H isomer, is also the only one of the compounds to exhibit a one-proton downfield signal (δ = 4.45).[6] In view of the conformational difference of the C(19) substituents in the D/E *cis* isomer pair as contrasted to the D/E *trans* pair the spin-spin coupling constants associated with the interaction of C(19)-H and C(20)-H would be expected to vary in the first set of isomers but stay constant in the second set. Indeed, inspection of the one-proton downfield octet (δ = 4.36–4.44), characteristic of C(19)-H coupling with C(20)-H and the methyl group, revealed J_{HH} to be 10.3 and 5.8 c.p.s. for VII and VIII, respectively, while 2.7 and 1.8 c.p.s. for V and VI. Tetrahydroalstonine's large J_{HH} value establishes a 19,20-*trans* diaxial configuration[7] for this alkaloid (VII) thus implying also a 19,20-*trans* arrangement for akuammigine (VIII). However, the consistently low values of the



V VI VII VIII

(1) This work was supported by a research grant (M-1301) from the National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare.

(2) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958), and references contained therein.

(3) E. Wenkert and N. V. Bringi, *ibid.*, **81**, 1474, 6553 (1959).

(4) N. Neuss and H. E. Boaz, *J. Org. Chem.*, **22**, 1001 (1957).

(5) This substance, m.p. 177°, was produced first by Harley-Mason and Waterfield (unpublished observation). We are indebted to Dr. Harley-Mason for this information and for a generous supply of alstonine and tetrahydroalstonial (II).

(6) Such equatorial C(3)-H systems as pseudoyohimbine, as contrasted to yohimbine (unpublished observations of this Laboratory), and some D/E *cis* Rauwolfia alkaloid derivatives (private communication from Dr. W. E. Rosen) show a similar signal.

(7) *Cf.* L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.

ajmalicines (V,VI) speak against a 19,20-*trans* diaxial configuration and, hence, limit them to a *cis* arrangement. As a consequence, the full constitution of the compounds under consideration is represented by the stereoformulas V–VIII.

The similarity of the non-aromatic portion of the p.m.r. spectra of aricine and reserpinine and that of tetrahydroalstonine (VII) shows these alkaloids to be ring A methoxy derivatives of VII.[4] Tetraphylline was identified as a derivative of ajmalicine (V) in a similar manner.

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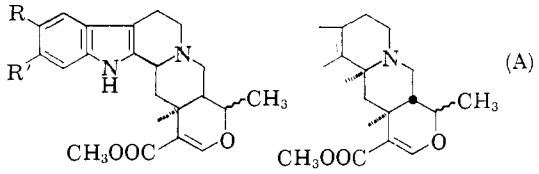
THE STEREOCHEMISTRY OF THE D/E RING FUSION IN THE HETEROYOHIMBINE ALKALOIDS

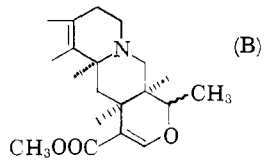
Sir:

A variety of physical and chemical data has been presented to date to support the assignment of a *trans*-D/E ring junction to the heteroyohimbine alkaloids of the tetrahydroalstonine group: tetrahydroalstonine (I), aricine (II), reserpinine (III), and 3-isoreserpiline (IV), and a *cis*-D/E junction in the ajmalicine group: ajmalicine (V), raumitorine (VI), and tetraphylline (VII).[1a,b,c,d]



(A)

	R	R′
I, V,	H	H
II, VI,	CH_3O	H
III, VII,	H	CH_3O
IV,	CH_3O	CH_3O



(B)

We now wish to present evidence for a reversal of this assignment. The rates of methiodide formation for a series of heteroyohimbines were followed by means of conductance measurements. In each case a 10-mg. sample of the alkaloid was dissolved in 10 cc. of acetonitrile. A conventional cell with black platinized electrodes was employed together with a resistance bridge, a 1,000 cps. oscillator, and an oscilloscope to find the balance point. The cell was maintained at 25 ± 0.5°, and nitrogen was bubbled through the solution. Approximately a five hundredfold excess of methyl iodide (1 cc.) was added so that the reaction followed pseudo first-order kinetics. At such a dilution the conductivity of the salt solution is proportional to the concentration of the salt. As the initial concentration of alkaloid is equal to the final concentration of methiodide salt, the first order rate expression, $-\ln c = kt - \ln c_0$, becomes $-\ln((1/R_\infty) - (1/R_t)) = kt - \ln(1/R_\infty)$, where c is the concentration of alkaloid at time t and c_0 is that at zero time, R_t is the resistance at time t and R_∞ that at the end of the reaction.

The rate constants, k, obtained from the plot of $-\ln((1/R_\infty) - (1/R_t))$ *vs.* t, for a series of heteroyohimbines are given in Table I.

TABLE I

PSEUDO FIRST-ORDER RATES OF METHIODIDE FORMATION AND pK_a VALUES OF ALKALOIDS

Alkaloids	$k \times 10^4$ sec.$^{-1}$	pK_a
Tetraphylline (VII)	27.0	6.37
Ajmalicine (V)	24.5	6.31
3-Isoreserpiline (IV)	1.51	6.07
Reserpinine (III)	1.36	6.01
Aricine (II)	1.21	5.70
Tetrahydroalstonine (I)	1.03	5.83
Apoyohimbine (VIII)	48.1	
Yohimbine (IX)	48.7	
Corynanthine (X)	74.9	
Alloyohimbine (XI)	13.8	

As all of the bases in Table I have been shown to possess an α-hydrogen at C-3,[1a,b,d] the fast rates exhibited by V and VII are compatible only with the *normal* configuration (A) for these compounds, where N_b is sterically unhindered. On the other hand, the slow rates of reaction of I, II, III, and IV, can be explained in terms of the *allo* configuration (B) where methiodide formation would lead to 1,3 steric interaction.

The above assignments were reinforced by rate studies in the yohimbine series. Thus apoyohimbine (VIII), yohimbine (IX), and corynanthine (X), all known to possess the *normal* configuration, exhibited very fast rates of reaction as shown in Table I, while alloyohimbine (XI) which belongs to the *allo* group was relatively slow. It is also evident from the data that *only rates within the same series of alkaloids should be compared.*

It follows from the present assignment that the D/E ring fusions in alstonine and serpentine must be *cis* and *trans*, respectively, and that isoreserpinine and reserpiline[1d] must belong to the *epiallo* series.

The pK_a's of the heteroyohimbine alkaloids in our possession (see Table I), determined in 66% dimethylformamide in water, show as expected that the less hindered *trans* compounds are more basic than the *cis* compounds. The pK_a values followed in general the order of the rate constants, but lacked the dramatic differences shown by the latter.

Conductance studies of the rates of formation of methiodides should give valuable information about the stereochemistry of alkaloids in general. Further studies with this technique are in progress in this laboratory, and a forthcoming publication

(1) (a) J. E. Saxton in "Alkaloids," Vol. VII, ed. R. H. F. Manske, Academic Press, New York, N. Y., 1960, pp. 59–62; (b) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1616 (1958); (c) A. Chatterjee and S. K. Talapatra, *Science and Culture (India)*, **20**, 568 (1955); (d) N. Neuss and H. E. Boaz, *J. Org. Chem.*, **22**, 1001 (1959).