

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 reserpine 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.

(8) Department of Chemistry, Indiana University, Bloomington, Ind.

DEPARTMENT OF CHEMISTRY
IOWA STATE UNIVERSITY
AMES, IOWA

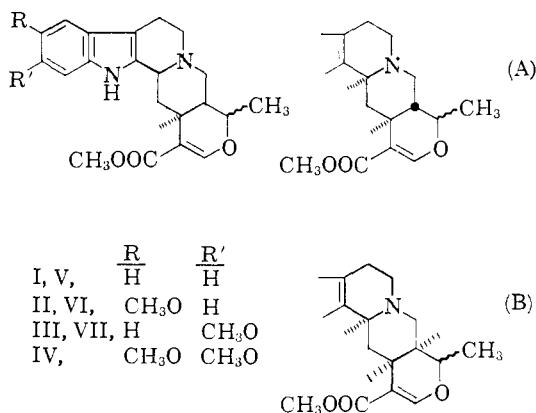
ERNEST WENKERT⁸
BÖRJE WICKBERG
CURTIS L. LEICHT

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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), reserpine (III), and 3-isoreserpiline (IV), and a *cis*-D/E junction in the ajmalicine group: ajmalicine (V), raumitorine (VI), and tetraphylline (V-II).^{1a,b,c,d}



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 $25 \pm 0.5^\circ$, and nitrogen was bubbled through the solution. Approximately a five hundredfold excess of methyl iodide (1 cc.) was added so that the reaction fol-

(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).

lowed 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
Reserpine (III)	1.36	6.01
Aricine (II)	1.21	5.70
Tetrahydroalstonine (I)	1.03	5.83
Apyohimbine (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_t 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 isoreserpiline 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

will describe the stereochemistry of the C-19 methyl group in the heteroyohimbine series.

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DEPARTMENT OF CHEMISTRY
THE PENNSYLVANIA STATE UNIVERSITY
UNIVERSITY PARK, PENNSYLVANIA

MAURICE SHAMMA
JANE B. MOSS

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BOOK REVIEWS

Monographs in Statistical Physics and Thermodynamics. Volume 2. Thermodynamics with Quantum Statistical Illustrations. By P. T. LANDSBERG, Professor of Applied Mathematics, University College, Cardiff, Great Britain. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1961. x + 499 pp. 16 × 23.5 cm. Price, \$14.50.

"Thermodynamics" by Landsberg is a welcome addition to the growing class of original monographs on theoretical thermodynamics. The opening three chapters, which comprise the meat of the volume, discuss the general theory. With the help of the conceptual apparatus of elementary topology, the author provides the most critical analysis yet available of the Carathéodory theory of entropy and absolute temperature and the thermodynamic theory of the third law. The fourth and fifth chapters, which we shall discuss later, are concerned with applications of the fundamental principles. A series of appendices amplifies some of the discussion in the preceding chapters. The book concludes with a selected bibliography with comments (it was amusing to note that, according to Landsberg, Gibbs' papers on thermodynamics were "published round about the turn of the century"). Worthwhile references are distributed throughout the volume. Many fine and unusual problems are inserted at appropriate intervals. A particularly valuable set is to be found on p. 95 where various shades of meaning of the terms "reversible" and "quasi-static" are analyzed.

It must not be thought that "Thermodynamics" is free from defects. Several criticisms can be leveled against it. The principal one is that the book is difficult to understand. This is due in part to a slightly ponderous style, but more profoundly it is related to the difficulty of maintaining mathematical rigor without loss of physical clarity. If deductive rigor is to be retained, it is necessary to adopt postulates and these are quite arbitrary from the mathematical viewpoint. However, if they are to be satisfactory to the physical scientist, they must represent idealizations of reality, preferably in the form of inductions from experiment. Landsberg understands this; yet the rationalizations which he presents for his postulates are not always entirely satisfactory. For example, the chemist may be dissatisfied with section 21 in Chapter IV on "the extension of thermodynamics to open and non-equilibrium systems." There, a vague and misleading impression is first given that open systems in equilibrium must be accorded the same treatment as systems not in equilibrium. Then, the important matter of defining the energy and entropy of open systems is evaded by the adoption of a definition (p. 129) of "simple" systems for which energy and entropy are asserted to exist and an assumption (p. 136) that many systems are simple. It is not clear whether his definition and assumption apply to electrochemical systems and other complex thermodynamic systems of interest. In this instance, generality has not hurt the mathematics, although it has resulted in a loss of physical clarity. Chapter IV, whatever its defects, is in the classical spirit of the earlier chapters. Chapter V on "Combinations of Thermodynamics and Statistical Mechanics" is, on the other hand, not in the same spirit, but is largely a sophisticated introduction to the statistical mechanics of ideal gases and radiation. In the later sections such diverse topics as "tempera-

ture dependent energy levels," "transition probabilities" and "thermodynamics as a precursor of quantum mechanics" are also discussed. The chapter is interesting and valuable, although it is not so penetrating as the first three and it does detract from the unity of the monograph.

Although it is not uniformly outstanding, "Thermodynamics" should be studied by every advanced student of theoretical thermodynamics and particularly by prospective authors of elementary textbooks on thermodynamics. Landsberg has surely achieved more than his modest ambition to "contribute something to our understanding of thermodynamics and to the exposition of its principles."

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF KANSAS
LAWRENCE, KANSAS

RICHARD J. BEARMAN

Free Radicals in Biological Systems. Proceedings of a Symposium held at Stanford University, March, 1960. Edited by M. S. BLOIS, JR., H. W. BROWN, R. M. LEMON, R. O. LINDBLOM and M. WEISSBLUTH. Academic Press Inc., 111 Fifth Avenue, New York 3, N. Y. 1961. xviii + 387 pp. 16 × 23.5 cm. Price, \$14.50.

The role of free radicals in biological systems is a question of considerable interest to biologists, chemists and physicists. The importance of the problem is evident from the list of biological processes in which free radicals have been put forward as decisive participants: enzymatic oxidation-reduction, photosynthesis, vision, carcinogenesis, radiation damage, synthesis of biological polymers and aging. The field has been in an increasingly active state of development especially since the development of the electron spin resonance (ESR) technique (1946) and the first use of this technique to observe free radicals in biological materials (1954). ESR studies have now led to detailed experimental evidence regarding the biological roles of free radicals. The widespread occurrence of free radicals in oxidation-reduction enzyme systems has been demonstrated. Detailed quantitative kinetic investigations of ESR signals in such enzyme systems have established new mechanisms and thermodynamic constants not available from conventional biochemical experiments. Characteristic ESR signals have been observed in photosynthetic systems and their kinetic properties analyzed. Free radicals have been observed in living animal tissues, and their relation to physiological processes described. A distinctive difference between free radical concentrations in normal and cancer tissue has been reported. The ESR technique has been used to demonstrate a clinically important difference between normal and pathological liver samples.

The field is in its infancy and many unsolved problems stand in the way of its further development. Among these are the need for ESR spectrometers capable of analyzing living systems with high sensitivity and high resolving power; improvement of methods for quantitation of ESR signals in terms of free radical concentration; development of criteria for associating an ESR signal with a particular substance in complex systems; techniques for observing short-lived ESR effects in irradiated tissues; methods for ESR observations on biological samples larger than 0.1 ml. (the present maximum); development of experimental strate-