hour fraction[10] showed that 64% of the physiological activity had been destroyed. Since only 15% of the methionine (position 4) and, therefore, also of the second serine (position 3) had been removed at 4.5 hours, neither of these units could have been involved in the loss of activity. Thus one, or both, of the first two amino acids in the sequence appear to be necessary for physiological activity.[11]

Acknowledgment.—The author wishes to acknowledge the technical assistance of Mr. A. M. Gross.

(10) As control, a sample of corticotropin-A was incubated for 4.5 hours in the buffer, but without aminopeptidase. No loss in activity was detected. The corticotropin-A sample used in this work had an activity of 110 units per milligram of peptide.

(11) An interesting sidelight on the aminopeptidase reaction was the effect of the hydrolysis on the solubility of corticotropin-A. At the concentration used in the experiment (5 mg./ml.), corticotropin-A is not completely soluble at *p*H 8.5. However, as the aminopeptidase reaction proceeded, the cloudy appearance of the reaction mixture became less pronounced and by 4.5 hours had cleared completely. Thus the first two amino acid units also appear to be associated with the solubility of corticotropin-A.

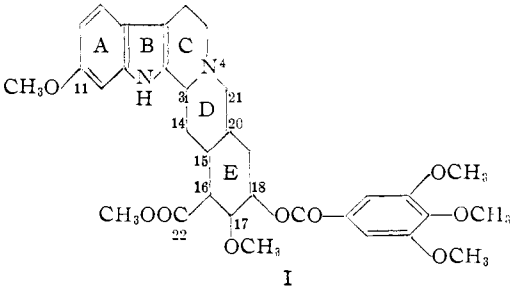
THE ARMOUR LABORATORIES
CHICAGO, ILLINOIS W. F. WHITE

RECEIVED JULY 22, 1955

THE STEREOCHEMICAL FORMULATION OF RESERPINE

Sir:

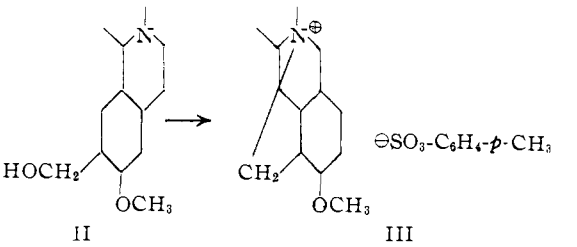
As an adjunct to studies taken up in the derivation of the gross structures for reserpine (I)[1,2] and deserpidine (I with the C-11 methoxyl replaced by hydrogen),[3] there was obtained in-



I

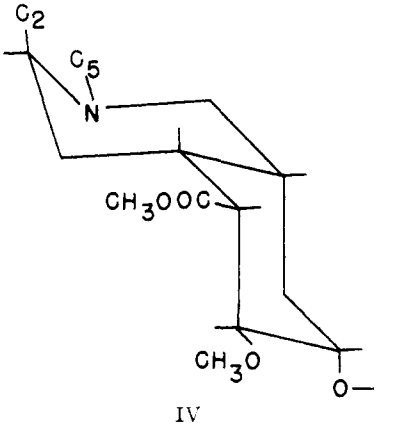
formation requiring for reserpine a *cis* nature for the substituents at C-16 and C-18[1] and also a *cis* juncture for the D and E rings.[4,5] We have now secured compelling evidence for a *cis* relationship of the hydrogens at C-16 and C-20, which, in turn, taken together with certain previously recorded observations, provides for the complete stereochemical formulation of this complex base.

Reserpinol (II) (Calcd.: C, 71.32; H, 8.16. Found: C, 70.96; H, 8.23), m.p. 254–255.5°, obtained by lithium aluminum hydride reduction of methyl reserpate tosylate (V),[1] was converted, on



II III

treatment with *p*-tosyl chloride in pyridine under normal conditions, to a high-melting (330–333°, dec.) solid which we consider to be the quaternary salt III (Calcd.: C, 66.39; H, 6.90. Found: C, 66.18; H, 6.88), by reason of the following characteristics: (i) infrared absorption at 8.2–8.6, 8.91, 9.62 and 9.86 μ, indicative of the *p*-tosyloxy anion,[6] (ii) ultraviolet absorption maxima at 222 mμ (log ϵ 4.70), 269 mμ (log ϵ 3.80) and 294 mμ (log ϵ 3.93), nearly identical with those of reserpinol hydrogen tosylate and therefore signifying an unmodified indole ring, and (iii) in 66% dimethylformamide, no titratable groups between *p*H 3 and 13, and recoverable after treatment, in solution, with alkali.[7] It is apparent that the salt III, which possesses a bridged bicyclic system defined by atoms 4 and 15 through 22, can result from N-4 attack on C-22 of the unisolated II-tosylate only if C-21 and the carbomethoxyl group originally present in reserpine are attached in a *cis* fashion to ring E. The above finding, coupled with the equatorial nature of the carbomethoxyl group as indicated by the stability of methyl reserpate to sodium methoxide in boiling methanol,[1] is incorporated in the expression IV for reserpine.



IV

Further, the demonstration that reserpine possesses the less stable configuration at C-3[3] implies that C-2 is joined through the *axial* bond of C-3, thereby placing the C-3 hydrogen equatorial and *trans* to the hydrogen at C-15 and C-20. Finally, the stereochemical course of elimination to methyl anhydroreserpate (VII) and the concurrent internal

(1) L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Muller, E. Schlittler, R. Schwyzer and A. F. St. André, *Helv. Chim. Acta*, **37**, 59 (1954).

(2) N. Neuss, H. E. Boaz and J. W. Forbes, THIS JOURNAL, **76**, 2463 (1954).

(3) H. B. MacPhillamy, L. Dorfman, C. F. Huebner, E. Schlittler and A. F. St. André, *ibid.*, **77**, 1071 (1955).

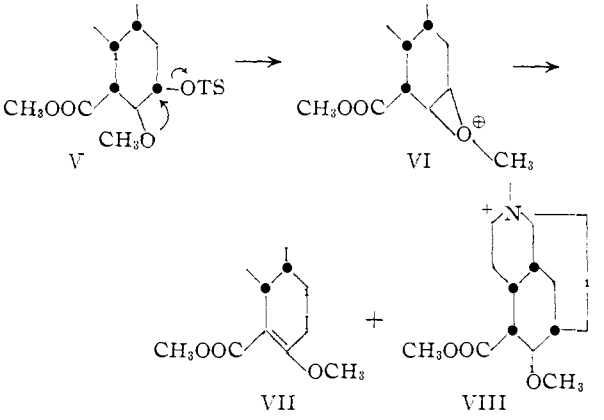
(4) P. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. Wintersteiner, *ibid.*, **77**, 2028 (1955).

(5) E. E. van Tamelen, P. D. Hance, K. V. Siebrasse and P. E. Aldrich, *ibid.*, **77**, 3930 (1955); see also reference (3).

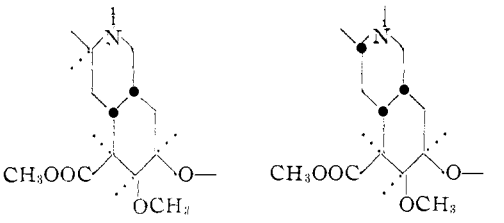
(6) F. L. Weisenborn and D. Burn, *ibid.*, **75**, 259 (1953).

(7) Formation of a higher molecular weight salt from II through intermolecular alkylation seems unlikely since yohimbyl alcohol monotosylate (R. C. Elderfield and A. P. Gray, *J. Org. Chem.*, **16**, 506 (1951))—wherein internal quarternization is sterically impossible—is recovered after being refluxed in benzene solution for two hours, and since methyl reserpate is not alkylated by isobutyl tosylate under similar conditions.

quaternization of methyl reserpate tosylate (V) can be most readily accommodated by neighboring group participation of a C-17 methoxyl placed *trans* to the groups at C-16 and C-18, proceeding through an intermediate oxonium salt (VI),[8] followed on the one hand by loss of a proton to yield VII and on the other hand by a *second* displacement at C-18 through backside attack by N-4, affording the quaternary salt VIII. Justification for this interpretation is offered by our observation that *trans*-2-methoxycyclohexylbenzenesulfonate, on being refluxed in collidine, is converted in significant yield to—among other products—cyclohexanone enol methyl ether, identified by hydrolysis to cyclohexanone.



The stereochemical expression IV stands in contrast to the two previously proposed for reserpine: IX by Schlittler, *et al.*,[3] and supported by Wintersteiner, *et al.*,[4] and more recently X, by Janot, Goutarel, Prelog, *et al.*[9] The internal quaternization of V, presumed to occur by simple



displacement with inversion at C-18,[4] was taken to indicate a *cis* relationship of the C-18 substituent and the C-15 and C-20 hydrogens, as expressed in both IX and X. This reaction, however, can be considered to proceed, as shown above, by *double-inversion with over-all retention of configuration* at C-18, consistent with the *cis* assignment to hydrogens at C-18 and C-20 (structure IV). The rotational evidence bearing on the relative configuration at C-3 and C-16 which led to the modification[9] of IX to X is automatically accommodated by the expression IV, which also places the C-16 hydrogen *trans* to that at C-3.

Acknowledgment.—Financial support for this investigation was provided by the Department of Health, Welfare and Education (Grant No. G-3892). The authors wish to express their appreciation to S. B. Penick and Co. for the gift of reserpine, and to H. Boaz of the Lilly Research Laboratories for the titration data.

(8) Elimination of V leading to VI requires in V a diaxial-type conformation at C-17 and C-18, which can result from IV through appropriate rotations in the ring system.

(9) M. M. Janot, R. Goutarel, A. LeHir, G. Tsatsas and V. Prelog, *Helv. Chim. Acta*, **38**, 1073 (1955).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WISCONSIN EUGENE E. VAN TAMELEN
MADISON, WISCONSIN PAUL D. HANCE

RECEIVED JULY 25, 1955

BOOK REVIEWS

Monographien zu Angewandte Chemie und Chemie-Ingenieur-Technik. Nr. 67. Verteilungsverfahren im Laboratorium. By ERICH HECKER, Max Planck Insitut für Biochemie, Tübingen, and ADOLF BUTENANDT, Max Planck Institut für Biochemie und Physiol.-Chem. Institut der Universität, Tübingen, Verlag Chemie, G.m.b.H., Weinheim/Bergstrasse, Germany. 1955. 229 pp. 15.5 × 23 cm. Price, $4.75.

While such laboratory methods of laboratory separation and purification as fractional distillation and chromatography have been well treated in monographs, there has been no whole book devoted to a comprehensive account of the theory and practice of liquid–liquid extraction. The need is now filled. This newest member of an important German series is authoritative, well-documented (525 references), and up to date (through 1953).

The book begins with the Nernst distribution law and a definition of multiplicative partition. Batchwise application of the latter is considered in detail, with descriptions of extraction batteries, the computation of theoretical partition curves, and the several recycling and withdrawal procedures, which are critically evaluated. Attention is centered on the fractionation of mixed solutes rather than on the mere transfer of a solute from one phase to another. The number of extraction stages is shown to depend on the separation factor, determined by the composition of the solute and the two solvent phases; the volume factor, determined by the relative volumes of the phases; the initial concentration of impurities; and the degree of purity desired in the product. Laboratory-scale continuous extraction also is treated, along with some aspects of partition chromatography.

The special part is essentially a review of the partition behavior of organic compounds classified according to structure, and metal ions classified as their neutral or anionic complexes. A kind of appendix gives mathematical derivations and pertinent numerical tables.

Quantitative relationships between partition behavior and constitution of solutes and solvents are mostly lacking, but the lack is also in present knowledge. A more serious possible flaw is the incompleteness of literature coverage. In spite of its extensive bibliography, the book cannot be trusted to supply all references to individual studies of apparatus or materials. It is the reviewer's impression that