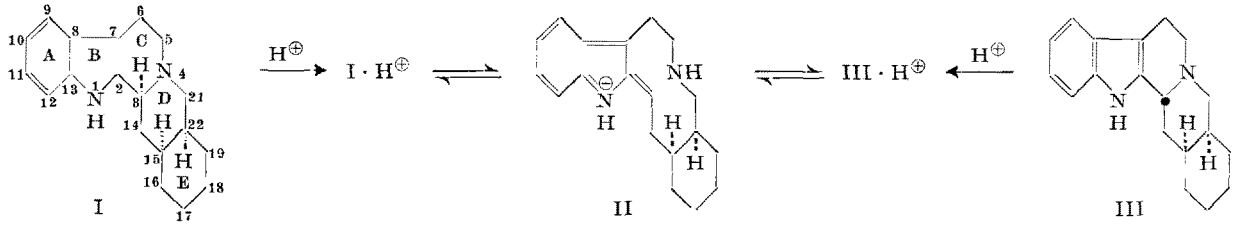
Brèves communications - Kurze Mitteilungen
Brevi comunicazioni - Brief Reports

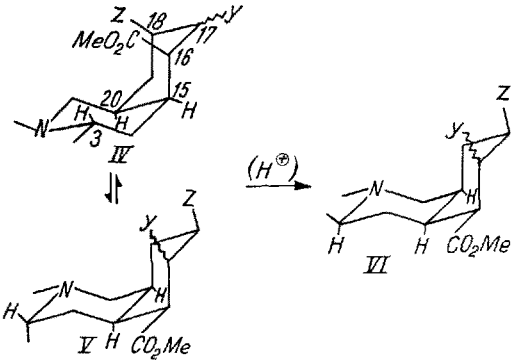
The Constitution of the Alloyohimbanes[1]

While the stereochemistry of the ring skeleta of the alkaloids alloyohimbine[2], α-yohimbine[2] (rauwolscine[3]), 3-epi-α-yohimbine[4], deserpidine[4] and reserpine[4] is based essentially on the assignment of an all-cis configuration to the hydrogenation product of the octadehydroyohimbane sempervirine[5] and of the synthetic Δ^3-dehydroalloyohimbane[6], this formulation is somewhat in jeopardy because of the alkaline nature of the reducing medium[7], and because of the fact that, as now can be reported, catalytic hydrogenation of sempervirine at pH 10 and 48 pounds pressure produced 55–66% *d,l*-alloyohimbane (I), m.p. 149–150° *as well as* 2,6% *d,l*-epialloyohimbane (III), m.p. 187–188°[8]. Despite their comparable energy content,–both compounds possessing in their favorable conformations two axial and one equatorial bridgehead hydrogen atoms–, I and III should be distinguishable by their different reactivity at C-3 and N^b. Thus their distinct difference in basicity: pK'_a (in 80% methylcellusolve) of 7·12, 7·13 for I and 7·48, 7·51 for III, the fact that III readily forms an amine oxide while I does not, and the fact that I can be dehydrogenated easily by palladium-maleic acid[9] in sharp contrast to III strongly support the presently accepted structures of allo- and epiallo-yohimbane.

Because of the importance of recent C-3 epimerisations in the alkaloid series[1], similar studies were undertaken on compounds I and III. Conc.-hydrobromic-acetic acid treatment of *either* isomer, proceeding by way of C(3)-N^b bond rupture (cf. II), yielded 74 ± 5% of a mixture containing 78 ± 1% III. On the other hand alkaline treatment of *either* compound under Huang Minlon conditions produced 78% of a mixture containing only 4% of isomerised amine. Increased basicity of the medium enhanced the conversion as well as the destruction of the compounds. These results signify that only acid-catalysed epimerisations readily attain equilibrium, and that only this type of data can be used safely as criterion for configurational assignments of the alkaloids.

The acid-induced conversion of deserpidine and reserpine to their allo epimers[1] clearly demonstrates that the alkaloids contain axially oriented C-16 and C-18 substituents (IVa) or preferably an axial C(2)-C(3) linkage (Va) while the allo compounds possess the more thermodynamically stable configuration VIa. The intramolecular formation of a quaternary ammonium salt from methyl reserpate 18-tosylate under essentially solvolytic conditions (collidine or dimethylformamide)[2] suggests strongly neighboring group participation by the 17-methoxyl in displacement and perhaps also elimination reactions at C-18. This requirement makes an all-trans arrangement of ring E substituents mandatory





a Y = OMe, Z = $OCOC_6H_2(OMe)_3$ *b* Y = OH, Z = H

[1] The financial support of this work by Ciba Pharmaceutical Products Inc. is acknowledged gratefully.

[2] A. LEHIR, C. r. Acad. Sci. *254*, 2613 (1952). – A. LEHIR, M. M. JANOT, and R. GOUTAREL, Bull. soc. chim. France *20*, 1027 (1953).

[3] A. CHATTERJEE and S. PAKRASHI, Naturwissenschaften *41*, 215 (1954). – A. CHATTERJEE, A. K. BOSE, and S. PAKRASHI, Chem. and Ind. *1954*, 491.

[4] H. B. MACPHILLAMY, L. DORFMAN, C. F. HUEBNER, E. SCHLITTLER, and A. F. ST. ANDRÉ, J. Amer. Chem. Soc. *77*, 1071 (1955).

[5] A. LEHIR, R. GOUTAREL, and M. M. JANOT, Bull. soc. chim., France *19*, 1091 (1952).

[6] G. STORK and R. K. HILL, J. Amer. Chem. Soc. *76*, 949 (1954).

[7] A. LEHIR, R. GOUTAREL, and M. M. JANOT, Bull. soc. chim., France *19*, 1091 (1952). – For a discussion of the change of the stereospecificity of catalytic hydrogenation with pH see A. L. WILDS, J. A. JOHNSON, Jr., and R. E. SUTTON, J. Amer. Chem. Soc. *72*, 5524 (1950).

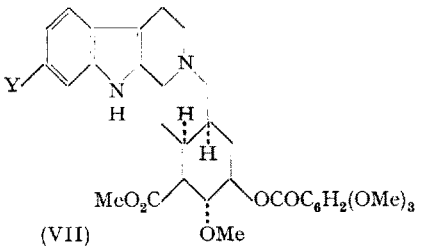
[8] The authors wish to thank Professor STORK for kindly sending them samples of the above two compounds for mixed melting point determination.

[9] R. MAJIMA and S. MURSHASHI, Proc. Imp. Acad. (Tokyo) *10*, 341 (1934). – The Majima method of ring C dehydrogenation has been found to be of general applicability and hence more useful than the lead tetracetate procedure.

[1] H. B. MACPHILLAMY, L. DORFMAN, C. F. HUEBNER, E. SCHLITTLER, and A. F. ST. ANDRÉ, J. Amer. Chem. Soc. *77*, 1071 (1955).

[2] P. A. DIASSI, F. L. WEISENBORN, C. M. DYLION, and O. WINTERSTEINER, J. Amer. Chem. Soc. *77*, 2028 (1955).

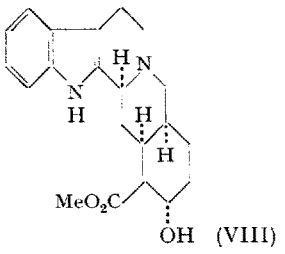
and limits the structure of reserpine and deserpidine to VII a and b.



(VII)

a: Y = OMe b: Y = H

The acid-catalysed 3-epi-α-yohimbine-to-rauwolscine transformation[1] indicates that the former has an axial carbomethoxy group (IVb) or an axial C(2)-C(3) linkage (Vb) while in the latter both functions are equatorially directed. The demethylation of deserpidinol to rauwolscinyl alcohol[1], with little likelihood of inversion at C-17, also points to a trans relationship of ring E substituents in α-yohimbine (VIII) and its C-3 epimer[2].



(VIII)

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Department of Chemistry, Iowa State College, Ames, (Iowa), June 17, 1955.

Zusammenfassung

Die zur Zeit angenommene stereochemische Formulierung von allo-Yohimban wird durch die Tatsache gestützt, dass epi-allo-Yohimban (III) eine stärkere Base als allo-Yohimban (I) ist. Ferner bildet III ein Aminoxyd, während I dies nicht tut. I wird katalytisch erheblich leichter zu einer quaternären Verbindung dehydriert als III. Zwischen I und III bildet sich ein säurekatalysiertes Gleichgewicht, das 78,7% III enthält. Diese Ergebnisse und eine neue Interpretierung der Verwandlung von Reserpsäuremethylestertosylat in eine quaternäre Ammoniumverbindung deuten darauf hin, dass dem Reserpin und dem Deserpidin die sterische Formel VII zukommen muss.

[1] H. B. MACPHILLAMY, L. DORFMAN, C. F. HUEBNER, E. SCHLITTLER, and A. F. ST. ANDRÉ, J. Amer. Chem. Soc. *77*, 1071 (1955).

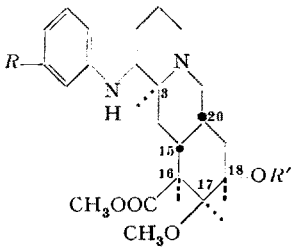
[2] Previous discussions of the configuration of alkaloids of the alloyohimbane type have been based on ambiguous steric hindrance phenomena[3] and on one case[4] on a non-existant di-chair cis-decahydroisoquinoline conformation.

[3] A. LEHIR, M. M. JANOT, and R. GOUTAREL, Bull. soc. chim. France *20*, 1027 (1953). – A. CHATTERJEE and S. PAKRASHI, Naturwissenschaften *41*, 215 (1954).

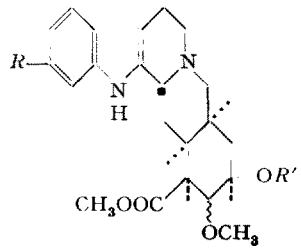
[4] A. CHATTERJEE, A. K. BOSE, and S. PAKRASHI, Chem. and Ind. *1954*, 491.

Rauwolfia Alkaloids XXI.
The Stereochemistry of Reserpine and Deserpidine

We have provisionally favored the stereochemical formula I for reserpine and deserpidine[1]. A recently reported experimental finding has been interpreted by another group of investigators[2] to indicate a similar formula. However, certain new facts have been obtained which establish the expression II as more nearly representing the stereochemistry of these alkaloids.



I



II

Reserpine: $R = -OCH_3$, $R' = -COC_6H_2(OCH_3)_3$

Deserpidine: $R = -H$, $R' = -COC_6H_2(OCH_3)_3$

It had previously been assumed that the driving force for the epimerization reaction at C-3 of reserpine and its derivatives and derivatives of deserpidine resided in the greater inherent stability of the alloyohimbane over the 3-epialloyohimbane skeleton[3]. However, further investigations revealed that the allo- and 3-epialloyohimbanes without asymmetric substitution at C-16, C-17 or C-18 under conditions of the isomerization are of approximately equal stability. For example, methyl anhydroreserpate[4] which must possess the allo configuration since it may be obtained from methyl 3-isoreserpate tosylate as well as from the normal tosylate, on treatment with acid, gives 11-methoxy-3-epialloyohimbone [m.p. 240–243°; $[\alpha]_D^{24}$ + 72° (chloroform). Calculated for $C_{20}H_{24}N_2O_2$: C, 74·04; H, 7·46; N, 8·64. Found: C, 73·88; H, 7·57; N, 8·49] as well as the previously described 11-methoxyalloyohimbone (reserpone)[5] in a ratio of 3 to 2. Furthermore it has been shown[6] that the composition of the system 3-epialloyohimbane-alloyohimbane at acid attained equilibrium is 3·6 to 1.

The reason for the complete epimerization of reserpine and its derivatives and certain derivatives of deserpidine must therefore lie in the steric relationship of the substituents in ring *E*. On the basis of I, the iso compounds (conformation III*a*) with 1,3-diaxial interactions not possessed by the normal compounds would be the less stable rather than the more stable of the pairs of epimers. However, the expression II (conformation IV*a*) gives

[1] H. B. MACPHILLAMY, L. DORFMAN, C. F. HUEBNER, E. SCHLITTLER, and A. F. ST. ANDRÉ, J. Amer. Chem. Soc. *77*, 1071 (1955).

[2] P. A. DIASSI, F. H. WEISENBORN, C. M. DYLION, and O. WINTERSTEINER, J. Amer. Chem. Soc. *77*, 2028 (1955).

[3] A. CHATTERJEE, A. K. BOSE, and S. PAKRASHI, Chem. and Ind. *1954*, 491.

[4] L. DORFMAN, A. FURLENMEIER, C. F. HUEBNER, R. A. LUCAS, H. B. MACPHILLAMY, J. M. MUELLER, E. SCHLITTLER, R. SCHWYZER, and A. F. ST. ANDRÉ, Helv. chim. Acta *37*, 59 (1954).

[5] C. F. HUEBNER, H. B. MACPHILLAMY, A. F. ST. ANDRÉ, and E. SCHLITTLER, J. Amer. Chem. Soc. *77*, 472 (1955).

[6] E. WENKERT and L. H. LIU, J. Amer. Chem. Soc. (in press). – We are indebted to Prof. WENKERT for communication of this fact to us before publication.