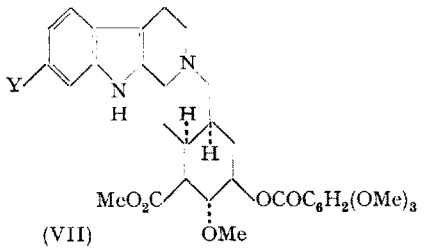
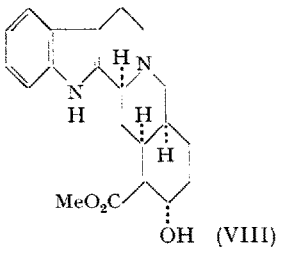
and limits the structure of reserpine and deserpidine to VII a and b.



(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)

E. WENKERT and LIANG H. LIU

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).

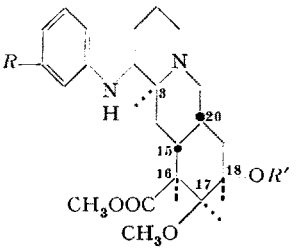
[2] Previous discussions of the configuration of alkaloids of the alloyohimbane type have been based on ambiguous steric hindrance phenomena[3] and on one case[4] on a non-existant di-chair cis-decahydroisoquinoline conformation.

[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).

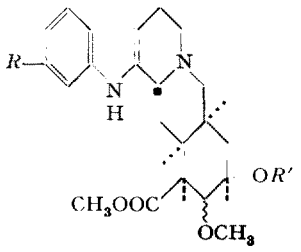
[4] A. CHATTERJEE, A. K. BOSE, and S. PAKRASHI, Chem. and Ind. *1954*, 491.

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).

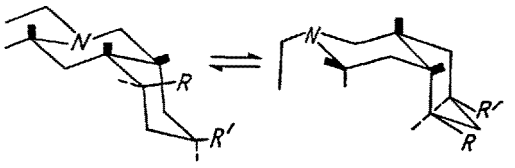
[3] A. CHATTERJEE, A. K. BOSE, and S. PAKRASHI, Chem. and Ind. *1954*, 491.

[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).

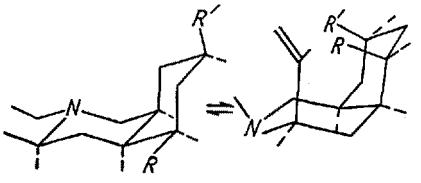
[5] C. F. HUEBNER, H. B. MACPHILLAMY, A. F. ST. ANDRÉ, and E. SCHLITTLER, J. Amer. Chem. Soc. *77*, 472 (1955).

[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.

a clear explanation for the greater stability of the iso compounds.



III



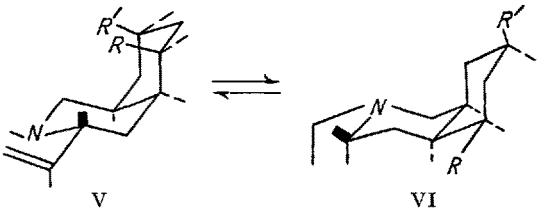
IV

a: $R = -COOCH_3$ $R' = -OCOC_6H_2(OCH_3)_3$
b: $R = -COOH$ $R' = OH$

Further, 3-iso-reserpic acid (as the nitrate) ([m. p. 266 to 270°]. Calculated for $C_{22}H_{28}N_2O_5 \cdot HNO_3 \cdot H_2O$: C, 54·88; H, 6·49; N, 8·73. Found: C, 55·07; H, 6·32; N, 9·01) on treatment with acetic anhydride-pyridine yielded an O-acetyl amino acid rather than a lactone as is obtained from reserpic acid hydrochloride. This amino acid with diazomethane gave methyl 3-iso-reserpate acetate[1]. On the basis of I, 3-isoreserpic acid possessing the conformation III*b* should readily lactonize whereas the new expression II (conformation IV*b*) for the iso compound would explain the greater difficulty encountered in lactone formation. Existence of the ring conversion isomer of IV*b* possessing substituents at C-16 and C-18 in the axial orientation required for closure to the lactone ring can be seen to be extremely unlikely in contrast to its counterpart III*b*. Lactone formation of IV*b* could, of course, also occur by transformation of ring *E* in one of its conversion isomers to the boat conformation but this requires extra energy and is not necessary in III*b*.

The absolute configuration established by KLYNE[2] for yohimbine indicates that the hydrogen at C-3 is in the α orientation. The contribution of such an axial hydrogen is shown by the differences in molecular rotation between a series of three yohimbane derivatives and their corresponding tetradehydro compounds. The values vary from − 586° to − 602°. The difference between a series of three alloyohimbane derivatives and their corresponding tetradehydro derivatives are likewise highly negative (− 267° to − 690°). Therefore, the hydrogen at C-3 in alloyohimbane is α and 3-epi-alloyohimbane possesses the absolute configuration at C-3, C-15 and C-20 indicated in II. This implies that the stereochemistry of alloyohimbane (C-3, C-15, C-20 cis) as indicated by LE HIR *et al.*[3] and STORK *et al.*[4] is accepted. By application of Hudsons lactone rule (KLYNE[5]) the groups at C-16 and C-18 are oriented in the β position in reserpine[6] and deserpidine (Δ lactone-acid = + 641 [pyridine])[1] which leads to II as the absolute configuration of these alkaloids.

Reserpine in solution can be regarded as an equilibrium mixture of the two ring conversion isomers V*a* and VI*a* based on the trans-anti-cis and cis-anti-cis ring skeletons with the latter being energetically preferred. The predominance of VI is also indicated by the behavior of reserpic acid lactone (V*b*) which is locked in the trans-anti-cis conformation and reserpinediol (VI*b*) towards catalytic dehydrogenation over palladium using maleic acid as a hydrogen acceptor[1]. The lactone is recovered in 70% yield under conditions which give a quantitative yield of tetradehydroreserpinediol. Access of the hydrogen atom at C-3 in V*b* to the catalyst surface would be expected to be somewhat hindered.



V VI

a: $R = -COOCH_3$, $R' = OCOC_6H_2(OCH_3)_3$
b: $R - R' = -\overset{O}{\overset{\|}{C}}O-$

a: $R = -COOCH_3$, $R' = OCOC_6H_2(OCH_3)_3$
b: $R = CH_2OH$, $R' = OH$

Clear cut evidence for the configuration at C-17 is not at hand since reactions involving this center can be variously interpreted. However, α-orientation of the methoxyl seems preferable because, among other reasons, β-orientation of this group would make formation of the quaternary salt from methyl reserpate tosylate[2] sterically difficult. We are indebted to Dr. D. PRINS for pointing this out to us[3].

C. F. HUEBNER, H. B. MACPHILLAMY, E. SCHLITTLER, and A. F. ST. ANDRÉ

Research Department, CIBA Pharmaceutical Products Inc., Summit, New Jersey, June 2, 1955.

Zusammenfassung

Für Reserpin und Deserpidin wird eine neue stereochemische Formulierung vorgeschlagen, die auf folgenden experimentellen Befunden beruht:

1. Reserpin- und Deserpidinderivate epimerisieren als 3-Epialloverbindungen vollständig zu den entsprechenden Isoverbindungen. Im Gegensatz dazu epimerisieren einfachere 3-Epialloyohimbane (ohne Substituenten in 16, 17 und 18-Stellung) zu einer Mischung von normaler und iso-Verbindung. Beide Isomere scheinen in diesem Fall ungefähr gleiche Stabilität zu besitzen.

2. Im Gegensatz zu Reserpsäure bildet iso-Reserpsäure kein Lakton.

3. Interpretation der Drehungswerte deutet darauf hin, dass das H-Atom in Stellung 3 und die Substituenten in Stellung 16 und 18 β-Orientierung besitzen.

[1] Paper XIX, H. B. MACPHILLAMY, C. F. HUEBNER, E. SCHLITTLER, A. F. ST. ANDRÉ, and P. R. ULSHAFER, J. Amer. Chem. Soc. (in press).

[2] W. KLYNE, Chem. and Ind. *1954*, 1032.

[3] A. LE HIR, R. GOUTAREL, and M. M. JANOT, C. r. Acad. Sci. *235*, 63 (1952).

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

[5] W. KLYNE, Chem. and Ind. *1954*, 1198.

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

[1] R. MAJIMA and S. MURAHASI, Coll. Papers Fac. Sci. Osaka *2*, 341 (1935).

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

[3] Prof. E. VAN TAMELEN has kindly given us a copy of a manuscript on the stereochemistry of reserpine prior to publication. The invalidity of I is pointed out and II is mentioned as one of two possibilities for the new representation of reserpine.