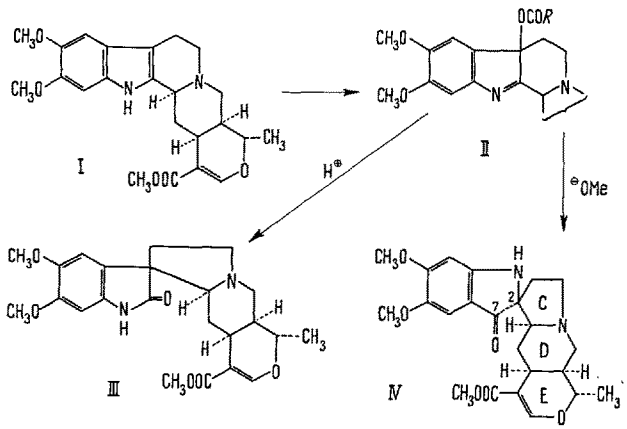
Rauwolfia Alkaloids XLVII
Isoreserpiline-ψ-Indoxyl, its Isolation, Synthesis and Structure

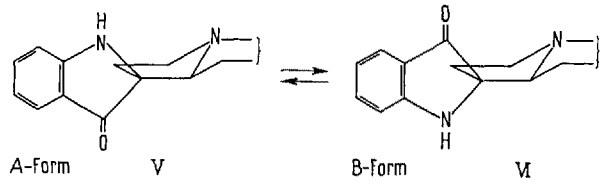
We have been concerned with methods for the conversion of yohimbinoid alkaloids into new derivatives which may on the one hand provide a simple way of determining the detailed structures of related compounds or on the other hand anticipate alkaloids yet to be reported[1]. Thus we have been able to prepare in a simple way, such oxindole alkaloids as mitraphylline, rhyncophylline[2] and carapanaubine[3] from their indole equivalents. In the latter case this was done by treating isoreserpiline with a lead tetra-acylate and a weak acid (I → II → III). We have observed that if acyloxyindolenines similar to II were treated with base[4] they were first methanolized to the corresponding hydroxyindolenines which subsequently rearranged more or less readily (this being a function of the C_3 stereochemistry[4]) to the ψ-indoxyls[5] (e.g. IV) making available for the first time a possible new class of alkaloids.



Up till now twenty four alkaloids have been isolated from *Rauwolfia vomitoria* Afzel. and the examination of the alkaloidal mother liquors continues to be a fruitful source of new bases. From the weak base fraction of ajmaline crystallization mother liquors we have obtained, by a combination of chromatography, nitrate salt precipitation and crystallization, a new yellow alkaloid along with reserpiline and isoreserpiline. This yellow compound, $C_{23}H_{28}O_6N_2$[6,7], had m.p. 251–254°, $[\alpha]_D^{25}$° −254° ($CHCl_3$); UV λ_{max} 224 mμ (ε 22,910, 251 (28,840), 283 (11,750) and 405 (5,600); IR ($CHCl_3$) bands in the carbonyl region at 1690, 1678, 1632 cm^{-1}, facts consistent with its formulation as isoreserpiline ψ-indoxyl (IV). Its fragmentation pattern in the mass spectrum was readily interpreted on this basis[8].

Isoreserpiline in methylene chloride with one equivalent of lead tetra *m*-bromobenzoate gave 7-*m*-bromobenzoyloxy-7H-isoreserpiline[9], m.p. 164–165° $[\alpha]_D^{25}$ + 135° ($CHCl_3$), λ_{max} 239 mμ (ε 47,860) and 294 (5,754), which upon reflux in methanolic sodium methoxide furnished the ψ-indoxyl IV in 25% yield, identical in all respects with the natural alkaloid. The stereochemistry is therefore defined at all positions except the spiro atom (C_2)[9] since the structure[10] of isoreserpiline is known with certainty.

Detailed studies with the more abundant yohimbine ψ-indoxyl[4] (m.p. 218°) $[\alpha]_D$ − 192° ($CHCl_3$), show that although it is unchanged in refluxing pyridine it does give rise in refluxing acetic acid to about 10% of an isomeric ψ-indoxyl which is instantly reconverted to the starting material in the presence of base. For the reasons outlined previously[2], this behaviour would be expected if the A-form (V) is more stable than the B-form (VI) and if the possible hydrogen bond in the conjugate acid is only weak. This receives support from the observation that while N_a methylation of yohimbine has little effect on basicity (pK_a 6.95 → 7.07 in 80% methyl cellosolve-water), the same alkylation of yohimbine ψ-indoxyl causes a marked decrease (pK_a 5.76 → 5.30) which is interpreted as being due to increased steric hindrance on the same side of the molecule as the lone pair orbital of N_b, i.e. the stereochemistry V. We therefore ascribe to reserpiline ψ-indoxyl the structure IV.



Zusammenfassung. Isoreserpiline-ψ-indoxyl wurde aus *Rauwolfia vomitoria* Afzel isoliert. Durch eine einfache Synthese, ausgehend von Reserpilin, wurde die Struktur dieses neuen Alkaloids bewiesen.

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Research Department, CIBA Pharmaceutical Company, a Division of CIBA Corporation, Summit (New Jersey, U.S.A.), March 25, 1963.

[1] Lectures given at the International Symposia on the Chemistry of Natural Products, Brussels, June 12, and Prague, August 31 (1962).
[2] N. FINCH and W. I. TAYLOR, J. Amer. chem. Soc. *84*, 1318, 3871 (1962).
[3] N. FINCH, C. W. GEMENDEN, I. H. HSU, and W. I. TAYLOR, J. Amer. chem. Soc., in press.
[4] N. FINCH, C. W. GEMENDEN, I. H. HSU, and W. I. TAYLOR, in preparation.
[5] Such rearrangements are well known in model compounds and in two classes of non-tetrahydro-β-carboline alkaloids (*inter alia*, B. WITKOP, Bull. Soc. Chim. France *1954*, 423.—M. F. BARTLETT, D. F. DICKEL, and W. I. TAYLOR, J. Amer. chem. Soc. *80*, 126 (1958)).
[6] Satisfactory analyses have been obtained for all compounds reported.
[7] The same alkaloid has also been recognized in *Rauwolfia ligustrina* Roem. et Shult. by J. M. MUELLER (private communication) and in *Aspidosperma discolor* A. DC. by N. DASTOOR and H. SCHMID, Exper. *19*, 297 (1963).
[8] This spectrum and those on related ψ-indoxyls were kindly obtained for us by C. DJERASSI and will be discussed in detail elsewhere[4].
[9] This nomenclature is analogous to that used previously[3]. The convention adopted to describe the stereochemistry of the spiro atom (C_2 in IV) is also the same as that used in the case of the oxindoles, *viz.*, the suffix A for the C_7 carbonyl below the plane of the CDE rings and B for the reverse[2].
[10] M. SHAMMA and J. B. Moss J. Amer. chem. Soc. *84*, 1739 (1962).