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ABSOLUTE STEREOCHEMISTRY OF YOHIMBINE AND RESERPINE[1]

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Abstract—The absolute configurations of yohimbine and reserpine based upon the optical rotation studies, but no chemical proof, have been indicated by formulae I and II respectively. In this paper, the Prelog's asymmetric synthesis is applied with success to yohimbine(I) and methyl reserpate(IV), thereby providing evidence for the correctness of the formulae. Furthermore, yohimbine is directly correlated with dihydrocorynantheane(XVII) of known absolute stereochemistry, conclusively establishing the absolute stereochemistry of a number of yohimbine alkaloids.

YOHIMBINE was first isolated by Hesse[2] from *Aspidosperma quebracho-blanco*, Schlecht., and was later found to be a main alkaloid of *Corynanthe yohimbe*, Schum.[3] The structure of yohimbine, including its stereochemistry, was completely elucidated by 1956,[4] and was subsequently confirmed by the total stereoselective synthesis by van Tamelen *et al.*[5] As for the absolute configuration of naturally occurring (+)-yohimbine, Klyne proposed the formula I by the method of molecular rotation differences.[6] The same conclusion was reached by Djerassi *et al.*,[7] who applied the method of optical rotatory dispersion to the alkaloid field.

On the other hand, reserpine(II) constituting a member of pentacyclic indole alkaloids as well as yohimbine, was first isolated from *Rauwolfia serpentina*, Benth., by Schlittler *et al.* in 1952,[8] who also first proposed the correct formula for this alkaloid.[9] Soon after the complete stereochemistry of reserpine was finely elucidated in 1955, its correctness was finally confirmed in the brilliant total synthesis achieved by Woodward *et al.*[10] The absolute stereochemistry of reserpine was also indicated by the formula II, proposed by Schlittler *et al.*[11] and independently by Diassi *et al.*[12] as a result of the application of Klyne's extension of Hudson's lactone rule to the molecular rotation difference between reserpic acid and reserpic lactone.[6]

[1] The preliminary communications of this paper appeared in *Chem. & Ind.* 948 (1961) and *Tetrahedron Letters*, 181 (1962).

[2] O. Hesse, *Ber. Dtsch. Chem. Ges.* **13**, 2308 (1880).

[3] L. Spiegel, *Chem. Ztg.* **20**, 970 (1896).

[4] G. F. Smith in *Chemistry of Carbon Compounds* (Edited by E. H. Rodd) Vol. IV, Part C, pp. 2088–2119. Elsevier (1960).

[5] E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm and P. E. Aldrich, *J. Amer. Chem. Soc.* **80**, 5006 (1958).

[6] W. Klyne, *Chem. & Ind.* 1032 (1953); W. Klyne, *Ibid.* 1198 (1954); P. E. Aldrich *et al.*, *J. Amer. Chem. Soc.* **81**, 2481 (1959).

[7] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956).

[8] J. M. Müller, E. Schlittler and H. J. Bein, *Experientia* **8**, 338 (1952).

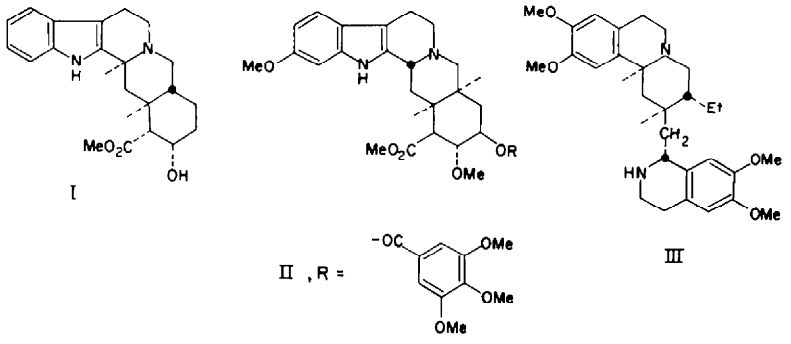
[9] L. Dorfman, C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André, *Experientia* **9**, 368 (1953).

[10] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958).

[11] C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St André, *Experientia* **11**, 303 (1955).

[12] F. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. Wintersteiner, *J. Amer. Chem. Soc.* **77**, 2028 (1955).

The purpose of the present work is the determination of the absolute stereochemistry of these alkaloids *by chemical means*, which implies the conversion of these natural products into the compound of known absolute stereochemistry, through a reaction sequence not affecting the configuration of the initial material.



In this connection, reference should be made to the absolute configuration of emetine(III) carried out in this laboratory[13] and confirmed at about the same time by Battersby *et al.*[14] and by van Tamelen *et al.*[15] Our conclusion was based upon the molecular rotation differences between 2′-acylemetine and 2′-acyl-5,11b-dehydroemetine, in that case the necessary references were made to the optical data[6,11,12] for determination of I and II for yohimbine and reserpine, respectively. Although the correctness of III for emetine is at present confirmed by Battersby who has chemically correlated the *ipecacuanha* with indole alkaloids,[16] it seemed desirable at that time to certify the absolute configuration of yohimbine alkaloids which were used by us as the standard for the determination of III for emetine.

Even though the chemical correlation of the configuration of one compound with that of another is usually a tedious and time-consuming task, it is often more reliable than the optical method.[17] Consequently, prior to the correlative work, the Prelog's asymmetric synthesis was first applied to determine the configuration at C_{17} of yohimbine(I) and C_{18} of methyl reserpate(IV).

Phenylglyoxylic acid chloride was added to a solution of yohimbine in pyridine to yield the ketoester(V), which was subjected to a Grignard reaction with methylmagnesium iodide to yield the hydroxyester(VI). This ester without further purification, afforded L-(+)-atrolactic acid(VIIa), $[\alpha]_D^{19}$ +1·50° (*c*, 15 in EtOH), $p^1\%$* 4·0,

*[1] p = a percentage of the excess of an antipode of atrolactic acid. W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *Helv. Chim. Acta* **36**, 325 (1953).

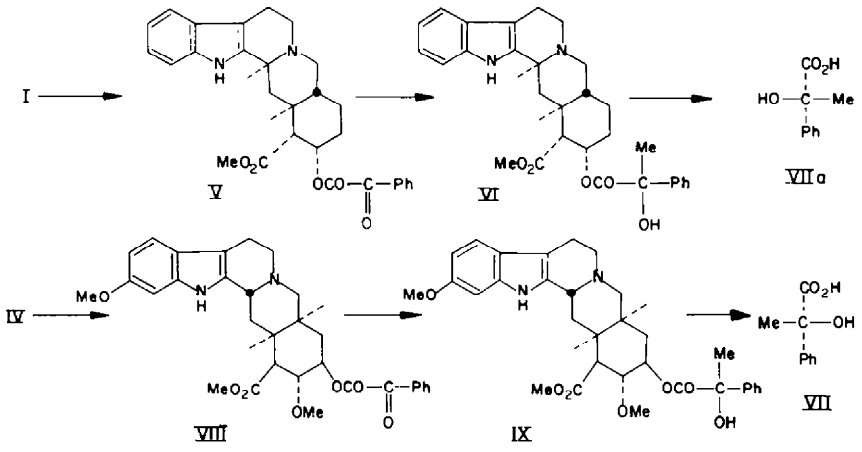
[13] Y. Ban, M. Terashima and O. Yonemitsu, *Chem. & Ind.* 568, 569 (1959); M. Terashima, *Chem. Pharm. Bull. Japan* **8**, 517 (1960).

[14] A. R. Battersby and S. Garratt, *Proc. Chem. Soc.* 86 (1959); *J. Chem. Soc.* 3512 (1959). A. R. Battersby, R. Binks and T. P. Edwards, *Ibid.* 3474 (1960).

[15] E. E. van Tamelen and J. B. Hester, *J. Amer. Chem. Soc.* **81**, 507 (1959); E. E. van Tamelen, P. E. Alderich and J. B. Hester, *Ibid.* **81**, 6214 (1959).

[16] A. R. Battersby and S. W. Breuer, *Abstracts* A, *I.U.P.A.C.* XIXth *International Congress of Pure and Applied Chemistry*, p. 159 (1963, London).

[17] E. E. Eliel, *Stereochemistry of Carbon Compounds*, pp. 87–123, p. 430. McGraw-Hill, New York (1962)



m.p. 89–91°, in 70% yield, which indicates that the hydroxyl group at C_{17} is α-oriented, supporting the formula(I) for yohimbine, in spite of the low magnitude of rotation of the present product (VIIa).

Reserpine(II) was partially hydrolysed to methyl reserpate(IV), which is known to have the same configuration as reserpine, since it may be esterified to the original alkaloid.[18] Methyl reserpate(IV) was mixed with phenylglyoxylic acid chloride to yield the unstable keto ester(VIII), which was purified only as the hydrochloride (VIII·HCl). The liberated free base was similarly subjected to a Grignard reaction with methylmagnesium iodide to yield the hydroxy ester(IX) in 76·6% yield, which was saponified to D-(−)-atrolactic acid (VIIb), $[\alpha]_D^{19}$ −9·78° (*c*, 6·5 in EtOH), p% 25·9, m.p. 88–90°. This result confirms that the hydroxy group at C_{18} is β-oriented, thereby lending further support to correctness of the formula II for reserpine.

The Prelog's rule for determination of configurations has been frequently applied to the steroids and terpenes, but the present work seems to constitute the first example of that rule applied to the alkaloids.

Concerning the structural relationships of pentacyclic yohimbine alkaloids to the tetracyclic ones such as corynantheine (X), dihydrocorynantheine (XI) and corynantheidine (XII), Woodward proposed an ingenious hypothesis for the biosynthesis of corynantheine as well as strychnine,[19] in which ring E of the precursor (XIII), either in the aromatic or in a reduced state, could split specifically between C_{17} and C_{18} to produce the basic ring system (XIV) of tetracyclic indole alkaloids. Ochiai and Ishikawa[20] correlated the latter bases with the cinchona alkaloids of known absolute stereochemistry.[21]

Furthermore, as to the biosynthesis of emetine (III), a norprotoberberine type of compound XV was assumed by Robinson[22] to undergo the Woodward fission between

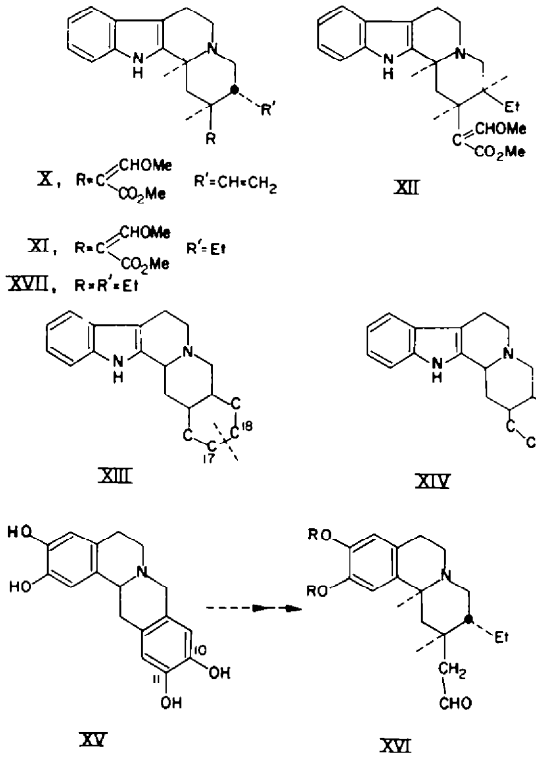
[18] R. E. Woodson, M. W. Youngken, E. Schlittler and J. A. Schneider, *Rauwolfia: Botany, Pharmacognosy, Chemistry & Pharmacology* p. 75. Little, Brown & Co., Toronto (1957)

[19] R. B. Woodward, *Nature* **162**, 155 (1948); R. Robinson, *The Structural Relations of Natural Products*. Clarendon Press, Oxford, (1955).

[20] E. Ochiai and M. Ishikawa, *Chem. Pharm. Bull. Japan* **7**, 386 (1959); *Tetrahedron* **7**, 228 (1959).

[21] V. Prelog and O. Häfliger, *Helv. Chim. Acta* **27**, 535, 545 (1944); *Ibid.* **33**, 2021 (1950).

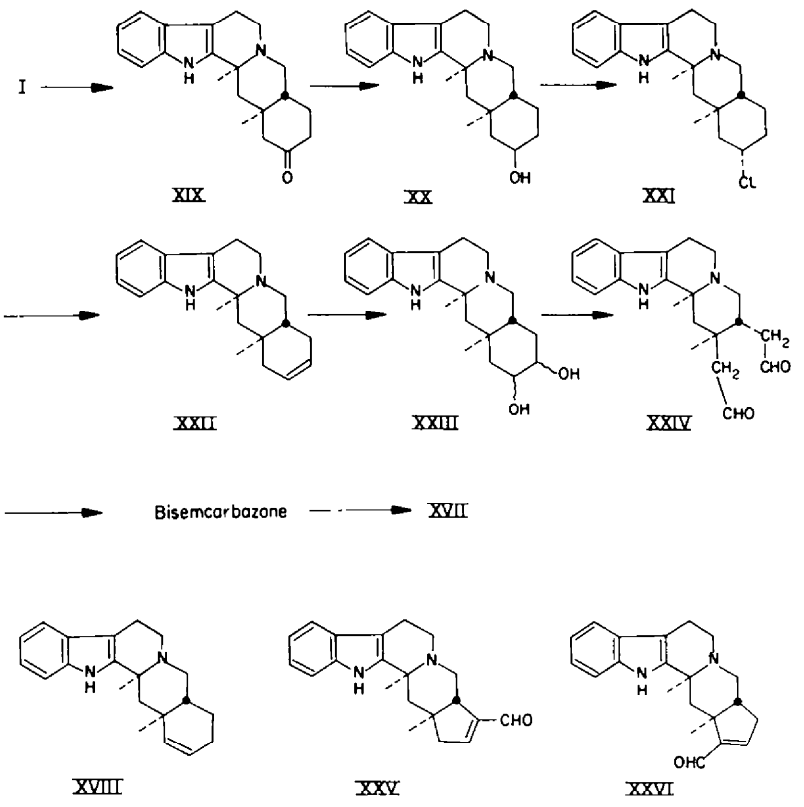
[22] R. Robinson, *Nature* **162**, 524 (1948).



C_{10} and C_{11}, exactly as in the case of the strychnine precursor, furnishing the aldehyde (XVI, R = H) after a reduction process of the side chain, which in turn, is condensed with DOPamine, followed by O-methylation to produce emetine (III). It is significant that protoemetine (XVI, R = Me) was isolated by Battersby *et al.*[23] from the extract of *Ipecacuanha* root, and that this alkaloid (XVI, R = Me) played a very important role in determining the relative and absolute stereochemistry of emetine. Based on this work, the Woodward fission with 17,18-dihydroxy-yohimbane (XXIII) correlated the yohimbine alkaloids with the tetracyclic indole alkaloids via the key intermediate, dihydrocorynantheane (XVII).

Consequently, yohimbine was oxidized with aluminum phenolate according to Witkop[24] to afford yohimbone (XIX), which was reduced with sodium borohydride to epiyohimbol (XX)[24,25] and the resulting product with phosphoryl chloride afforded 17α-chloroyohimbane (XXI). The halogenation did not proceed with other reagents such as PCl_5, $SOCl_2$ and PBr_3. The foregoing chloride (XXI) was heated with collidine in a sealed tube at 250° to yield Δ^{17}-yohimbene (XXII), m.p. 201–203°, $[\alpha]_D^{24}$ −197·6° in 60% yield. On assignment of this olefinic structure (XXII), the possibility of formation of Δ^{16}-yohimbene (apocorynanthol) [XVIII, Janot and Goutarel[26] recorded m.p. 171°, $[\alpha]_D$ −188° (EtOH)], was excluded judging from the m.p. of the present product

[23] A. R. Battersby, G. C. Davidson and B. J. T. Harper, *J. Chem. Soc.* 1774 (1959).
[24] B. Witkop, *Liebigs Ann.* **554**, 83 (1943).
[25] A. Chatterjee, A. K. Bose and S. Pakrashi, *Chem. & Ind.* 491 (1954).
[26] M. M. Janot and R. Goutarel, *Bull. Soc. Chim. Fr.* 509 (1949).



and the following reaction sequence which yielded only dihydrocorynantheane (XVII). When heated over 270°, carbonization occurred affording no product, which suggests that the preceding reaction conditions should be closely followed. Also, when the chloride (XXI) was heated with potassium hydroxide in ethanol, the same product (XXII) as above was obtained, but in a very low yield. An attempt to obtain the same product from the tosylate or the benzoate of epiyohimbol (XX), resulted in failure.

Subsequently, when osmium tetroxide was added to a solution of Δ^{17}-yohimbene (XXII), the black-brown osmic acid ester was deposited in a good yield, which with hydrogen sulfide or sodium sulfite yielded dihydroxyyohimbane (XXIII), m.p. 222°, $[\alpha]_D^{25}$ −82·4° as colorless hygroscopic needles. The hydrogen sulfide procedure of this decomposition was suggested by Professor van Tamelen, and is the preferred method even though the yield was only 27% of crude product (no doubt due to further oxidation of the indole part of the molecule).

The glycol cleavage followed by the Wolff–Kishner reduction, presented difficulties in that the resulting dialdehyde (XXIV) undergoes self aldol condensation to an α,β-unsaturated aldehyde (either XXV or XXVI). To avoid this unfavorable cyclization, 17,18-dihydroxy-yohimbane (XXIII) was oxidized with periodic acid to afford the dialdehyde (XXIV, $IR_{\nu,\,Nujol}$ 1714, 2740 cm^{-1}) in 85% yield, and converted into the bisemicarbazone, $IR_{\nu,\,Nujol}$ 1672, 1589 cm^{-1}. When, however, the diol was treated with sodium periodate, a crude product possessing an absorption band at 1675 cm^{-1}, but not at 1714 cm^{-1} was obtained, clearly demonstrating that the first formed product

changed into an α,β-unsaturated aldehyde (XXV or XXVI) as a result of an intramolecular aldol condensation. The same reaction was avoided by keeping the mixture anhydrous during the Wolff–Kishner reduction, in which procedure the foregoing semicarbazone was heated with 100% hydrazine and potassium hydroxide to afford a crude base. After chromatography and recrystallization, XVII was obtained as colorless needles, m.p. 182·5–184° (lit. m.p. 188·5° recorded by Prelog *et al.*[27]); $[\alpha]_D$ −96·6° (*c*, 0·1945 in pyridine) (lit. Prelog[27] $[\alpha]_D$ −96° (pyridine); Wenkert,[28] $[\alpha]_D$ −94° (pyridine)).

Professors Ochiai and Ishikawa kindly supplied an authentic sample of dihydrocorynantheane (m.p. 183·5–185° (uncorr.) measured by us. $[\alpha]_D$ −38° (methanol)) and its IR absorption spectral data for direct comparison with those of our product. The identity of both samples was proved by the superimposable IR spectra, the mixed m.p. (182·5–184·5°) and the identical R_f values, 0·87 (n-BuOH:AcOH:H_2O = 10:2:7), 0·95 (n-BuOH:EtOH: conc. NH_4OH:H_2O = 10:1:1:5) on paper chromatography.

Since the absolute configuration of dihydrocorynantheane was previously established by Ochiai and Ishikawa[20] and by Wenkert and Bringi,[28] and the relative stereochemistry of yohimbine was known,[4] the present correlation means that the configurations at C_3, C_{15} and C_{20} of yohimbine are the same as those of dihydrocorynantheane (XVII), that is to say, yohimbine has the formula I in terms of absolute configuration and this confirms the conclusion obtained by the optical method.[6] Furthermore, as yohimbine has been correlated with reserpine[29] via deserpidine[30] and α-yohimbine,[29] this work also supports the absolute configuration given to a number of yohimbine alkaloids.

EXPERIMENTAL[31]

Yohimbine phenylglyoxylate (V). To a solution of yohimbine (I; 550 mg) in pyridine (18 ml), phenylglyoxylic acid chloride (0·5 ml) was added under ice cooling. Immediately after the initiation of addition, the color of the solution turned red. The whole was allowed to stand overnight, poured onto ice water and basified with $NaHCO_3$ aq to produce the precipitate which was collected by filtration, washed with water and dried to yield a crude product (V; 700 mg). Recrystallized from hydrous acetone, it gave colorless needles, m.p. 246–248°, $[\alpha]_D^{22}$ +86·4° (*c*, 1·16 in $CHCl_3$), yield 552 mg (73%). $IR_{\nu C=O}$ 1730, 1683 cm^{-1}. (Found: C, 71·40; H, 5·81; N, 5·57. $C_{30}H_{30}N_2O_5$ requires: C, 71·59; H, 6·22; N, 5·76%).

Yohimbine atrolactate (VI). To an ethereal solution of MeMgI (prepared from Mg 584 mg, 24 mmoles; MeI, 3·408 g and absolute ether, 60 ml), was added a solution of the foregoing ester (V; 2·918 g, 6 mmoles) in tetrahydrofuran (60 ml) under mechanical stirring and ice-cooling over a period of 15 min. Immediately after the beginning of addition, a white powder was precipitated. The whole mixture was stirred at a room temp for 15 min and then stirred and refluxed at 60–70° for 3 hr. After cooling, the whole was poured onto ice water (100 ml) containing NH_4Cl (18 g), extracted with ether–tetrahydrofuran (1:1) 4 times. The extract was dried (Na_2SO_4) and the solvent removed to give a pale red semi-solid product (VI; 2·88 g, 95%) in a crude state. $IR_{\nu OH}$ 3360, $IR_{\nu C-O}$ 1729 cm^{-1}.

Atrolactic acid (VIIa). To a solution of KOH (2 g) in H_2O (6 ml) and methanol (34 ml) was added the foregoing crude hydroxy ester (VI; 2·86 g, 5·7 mmoles), and the whole mixture refluxed

[27] M.-M. Janot, R. Goutarel and V. Prelog, *Helv. Chim. Acta* **34**, 1207 (1951).
[28] E. Wenkert, and N. V. Bringi, *J. Amer. Chem. Soc.* **81**, 1474 (1959).
[29] E. Wenkert, E. W. Robb, and N. V. Bringi, *J. Amer. Chem. Soc.* **79**, 6570 (1957).
[30] L. Dorfmann, G. F. Huebner, E. Schlittler and A. F. St. André, *J. Amer. Chem. Soc.* **77**, 1071 (1955).
[31] M.ps are uncorrected. U.V. spectra were run on a Beckman DK-2 spectrophotometer and I.R. spectra in Nujol mulls on a JASCO DS-301 double-beam spectrophotometer equipped with NaCl optics.