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THE ABSOLUTE STEREOCHEMISTRY OF YOHIMBINE BY CHEMICAL CORRELATION WITH DIHYDROCORYNANTHEANE

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IN a previous communication,[1] we described an application of the Prelog's asymmetric synthesis[2] to the alkaloid field, thereby providing evidence for the correctness of the absolute configuration of yohimbine based upon the optical rotation studies.[3]

We wish at this time to report that yohimbine (I) has been directly correlated with dihydrocorynantheane (IX) of the known absolute stereochemistry.[4]

Yohimbine (I) was converted into epiyohimbol (III)[5,6] via yohimbone (II).[5] This alcohol (III) was refluxed with phosphoryl chloride in pyridine for 2 hr to afford 17α-chloroyohimbane (IV), colourless neddles (from methanol), d.p. 179-182°, $[\alpha]_D^{26}$ -60.7° (c, 0.28 ethanol). (Found: C, 72.94;

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[1] Y. Ban and O. Yonemitsu, Chem. & Ind. 948 (1961).

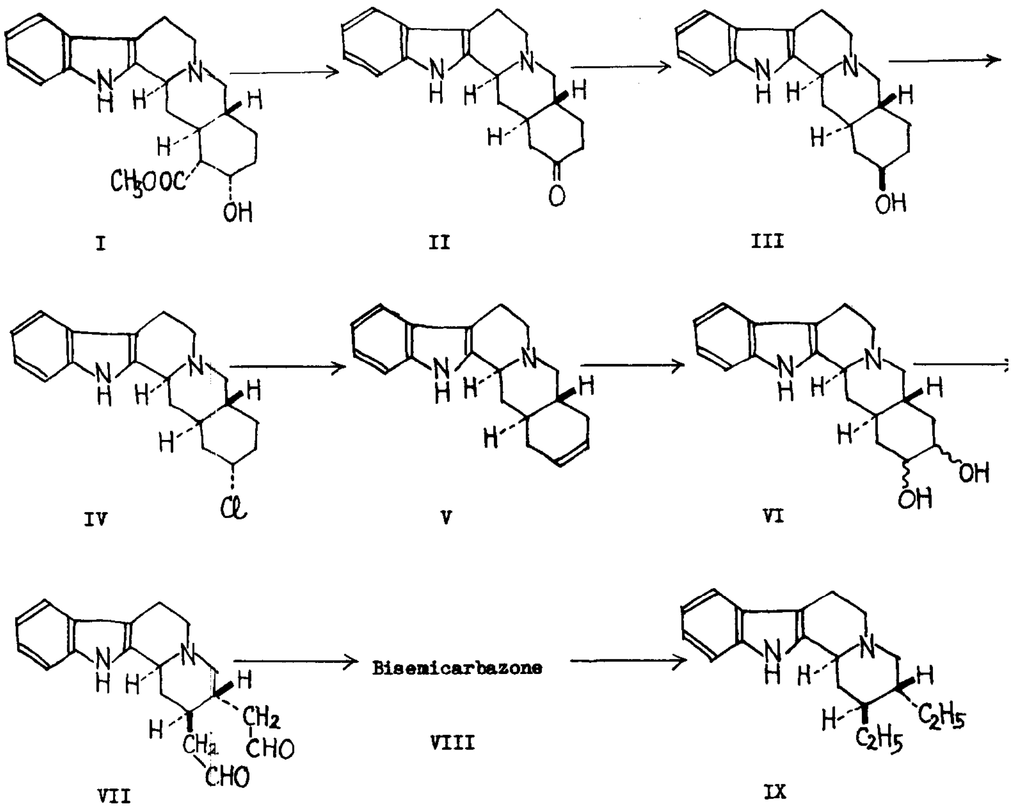
[2] V. Prelog, Helv. Chim. Acta 36, 308 (1953).

[3] W. Klyne, Chem. & Ind. 1032 (1953); W. Klyne, Ibid. 1198 (1954); P.E. Aldrich et al., J. Amer. Chem. Soc. 81, 2481 (1959); C. Djerassi, R. Riniker and B. Riniker, Ibid. 78, 6362 (1956).

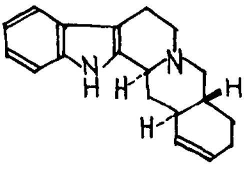
[4] E. Ochiai and M. Ishikawa, Chem. & Pharm. Bull. Japan, 7, 386 (1959); Tetrahedron 7, 228 (1959); E. Wenkert and N.V. Bringi, J. Amer. Chem. Soc. 81, 1474 (1959): cf. V. Prelog and E. Zalan, Helv. Chim. Acta 27, 535, 545 (1944); V. Prelog and O. Häfliger, Ibid. 33, 2021 (1950).

[5] B. Witkop, Liebigs Ann. 554, 83 (1943).

[6] A. Chatterjee, A.K. Bose and S. Pakrashi, Chem. & Ind. 491 (1954).



I II III IV V VI VII VIII IX



X

H, 7.62; N, 8.82; Cl, 11.18. $C_{19}H_{23}N_2Cl$ requires: C, 72.48; H, 7.36; N, 8.90; Cl, 11.26%), which was heated with collidine in a sealed tube at 250° for 7 hr to yield Δ^{17}-yohimbene (V) in 59.6% yield, colourless needles after chromatography over alumina and recrystallization from methanol, m.p. 201-203°, $[\alpha]_D^{24}$ -197.6° (c, 0.34 ethanol). (Found: C, 81.79; H, 8.15; N, 10.17. $C_{19}H_{22}N_2$ requires: C, 81.97; H, 7.96; N, 10.10%). The possibility of contamination of the product with Δ^{16}-yohimbene (apocorynanthol) (X) [Janot[7] recorded m.p. 171°, $[\alpha]_D$ -188° (ethanol)] was excluded based on the melting point of our product and the following reaction sequence, which yielded dihydrocorynantheane (IX). Hydroxylation of V by means of osmium tetraoxide yielded the diol (VI), colourless hygroscopic needles, m.p. 222°, $[\alpha]_D^{25}$ -82.4° (c, 0.505 ethanol). (Found: C, 72.65; H, 7.84; N, 9.57. $C_{19}H_{24}O_2N_2$ requires: C, 73.05; H, 7.74; N, 9.00%). The diol (VI) was oxidized with periodic acid at 0° for 1 hr to give the crude dialdehyde (VII), pale brown caramel (85%), I.R.: υ_{Nujol} 1714, 2740 cm^{-1}(-CHO), which without purification was converted into bisemicarbazone, a yellowish amorphous solid (70%), d.p. 199° (after softening at 170°), I.R.: υ_{Nujol} 1672, 1589 cm^{-1}. When, however, the diol was treated with sodium periodate at room temperature for one day, there was obtained a crude product possessing absorption at 1675 cm^{-1}, but not at 1714 cm^{-1}, suggesting that it is probably an αβ-unsaturated aldehyde which is a cyclization product of VII.[8] The bisemicarbazone (VIII) was heated with 100% hydrazine and potassium hydroxide in diethylene glycol at 160-170° for 5 hr to give a crude base (60.7%), which was chromatographed on alumina and then recrystallized twice from methanol to yield the colourless needles (IX), m.p. 182.5-184° (uncorr.) [Prelog[9] reported, m.p. 188.5°], $[\alpha]_D^{20}$ -96.6° (c, 0.1945 pyridine), [Prelog[9], $[\alpha]_D$ -96° (pyridine); Wenkert[10], $[\alpha]_D$ -94° (pyridine)]. (Found: C, 80.42; H, 9.04; N, 9.31. $C_{19}H_{26}N_2$ requires: C, 80.80; H, 9.28;

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[7] M.-M. Janot and R. Goutarel, Bull. Soc. Chim. Fr. 509 (1949).

[8] R.B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W.M. MacLamore, J. Amer. Chem. Soc. 74, 4223 (1952).

[9] M.-M. Janot, R. Goutarel and V. Prelog, Helv. Chim. Acta 34, 1207 (1951).

[10] E. Wenkert and N.V. Bringi, J. Amer. Chem. Soc. 81, 1474 (1959).

N, 9.92%).

Professors Ochiai and Ishikawa kindly supplied an authentic sample [m.p. 183.5-185° (uncorr.) measured by us. $[\alpha]_D$ -38° (methanol)] of dihydrocorynantheane (IX) and its infra-red spectral data for direct comparison with ours. The identity of both samples was proved by the superimposable infra-red spectra, mixed melting point (182.5-184.5°) determination and the identical R_f values, 0.87 (n-BuOH : AcOH : H_2O = 10:2:7), 0.95 (n-BuOH : EtOH : c.NH_4OH : H_2O = 10:1:1:5).

Since the absolute configuration of dihydrocorynantheane (IX) is established by correlation with dihydrocinchonine[4] and the relative configuration of yohimbine is unequivocally elucidated[11] particularly by the stereospecific total synthesis,[12] the absolute stereochemistry of yohimbine (I) is conclusively established by this correlation.

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[11] M.-M. Janot, R. Goutarel, A. Le Hir, A. Amin and V. Prelog, Bull. Soc. Chim. Fr. 1085 (1952); R.C. Cookson, Chem. & Ind. 337 (1953); W. Klyne, Ibid. 1032 (1953).

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