Total Synthesis of (±)-Coronaridine and an Improved Synthesis of (±)-Ibogamine

By SHOICHI HIRAI, KYOZO KAWATA, and WATARU NAGATA*

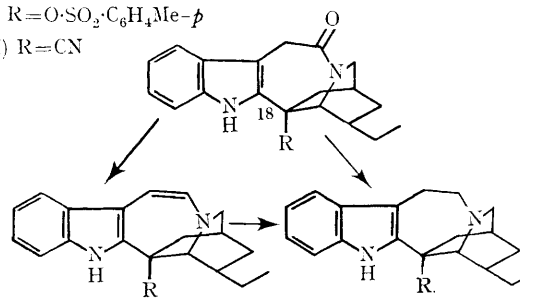
(*Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan*)

IN a previous communication,[1] we described the total synthesis of (±)-ibogamine with 7-oxo-18-tosyloxyibogamine (I) as a key intermediate. The work has now been extended to a total synthesis of (±)-coronaridine (VI),[2] and a one-step route to (±)-ibogamine (VII) from the same intermediate. Treatment of (I) with potassium cyanide in boiling acetonitrile for 15 hr. gave the anticipated lactam nitrile (II) (25%) [m.p. 270—280°; ν_{max} ($CHCl_3$) 3440, 2220, 1655, 1475, and 1408 cm.$^{-1}$]. Reduction of this nitrile with an excess of AlH_3 at −70° followed by dehydration of the resulting carbinolamine (II; 7ξ-OH instead of O) using alumina yielded the cyano-enamine (III) (87%) [m.p. 199—201°; ν_{max} ($CHCl_3$) 3446, 2220, 1628, and 1463 cm.$^{-1}$; λ_{max} (95%, EtOH) 234 (27,000)

and 277 mμ (11,200)]. Under these reduction conditions the hindered 18-cyano-group remained unchanged.

Catalytic hydrogenation of (III) in methanol gave 18-cyanoibogamine (IV) (80·7%) [amorphous; ν_{max} ($CHCl_3$) 3446, 2220, and 1463 cm.$^{-1}$] together with a small amount of 18-methoxyibogamine (V) [m.p. 152—154°; ν_{max} ($CHCl_3$) 3460, 1463, 1080, and 1056 cm.$^{-1}$], presumably formed by solvolysis of the pseudo-halogen nitrile group. Hydrolysis[3] of the compound (IV) with potassium hydroxide in diethylene glycol at 160° followed by careful acidification at low temperature and esterification with diazomethane furnished (±)-coronaridine (VI) (46%) [amorphous; ν_{max} ($CHCl_3$) 3450, 1725, 1465 cm.$^{-1}$, hydrochloride m.p. 225—227°; λ_{max} (95%, EtOH) 223·5 (32,900), 278·0 (8250), 285·5 (9030), and 294·0 mμ (7720)]. The free base and the hydrochloride were compared with natural specimens.† From identity of i.r., u.v., and mass spectra, and t.l.c. of both synthetic and natural specimens, (VI) was proven to be a racemic form of coronaridine. Next, in continuation of the previous work in which 7-oxo-18-tosyloxyibogamine (I) was transformed to (±)-ibogamine (VII) by a 5-step sequence, we have investigated a more direct route to the latter and found that (I) could be successfully converted into (VII) in 37–46% yield by AlH_3 reduction under the same conditions as used for the reduction of (II) to the carbinolamine. The marked contrast between the reduction products in the two cases is noteworthy.

(I) R=O·SO_2·C_6H_4Me-*p*
(II) R=CN



(III) R=CN

(IV) R=CN
(V) R=OMe
(VI) R=CO_2Me
(VII) R=H

(*Received, June 4th*, 1968; *Com.* 719.)

† We thank Dr. N. Neuss of the Lilly Research Laboratories for an authentic specimen of coronaridine hydrochloride.

[1] W. Nagata, S. Hirai, T. Okumura and K. Kawata, *J. Amer. Chem. Soc.*, 1968, **90**, 1650.
[2] (a) For a previous total synthesis see J. P. Kutney, W. J. Cretney, P. L. Quesne, B, McKague, and E. Piers, *J. Amer. Chem. Soc.*, 1966, **88**, 4756; (b) For a partial synthesis of voacangine see G. Büchi and R. E. Manning, *J. Amer. Chem. Soc.*, 1966, **88**, 2532.
[3] *Cf.* ref. 2b.