The Total Synthesis of (±)-Ibogamine

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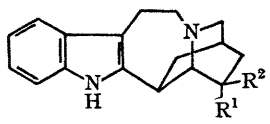
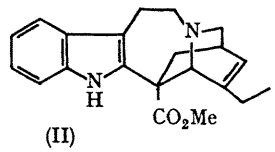
(±)-IBOGAMINE (Ia) was synthesized independently by Büchi,[1] Kutney,[2] Nagata,[3] and Sallay.[4] We also reported the synthesis of (±)-epi-ibogamine (Ib),[5] and recently the biogenetic-type synthesis of (±)-catharanthine (II) has been achieved by Scott.[6] We have now extended our method to the synthesis of (±)-ibogamine(Ia), which involves separation of the stereoisomers of the penultimate products (VI).

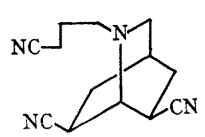


(I)a; R^1=H, R^2=Et
b; R^1=Et, R^2=H

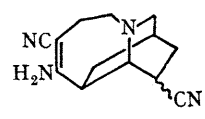


(II)

The Ziegler cyclization of (III),[5] obtained in four stages from 3-cyanopyridine, gave a complicated mixture of products, which was separated by silica gel chromatography to give two enamines: (IVa) m.p. 163—164° (recrystallized from ethyl acetate), i.r. (Nujol) 2240, 2180 cm.$^{-1}$, in 37% yield; and (IVb) m.p. 240—246° (recrystallized from ethyl acetate), i.r. (Nujol) 2225(w), 2170(s) cm.$^{-1}$, in 10% yield.

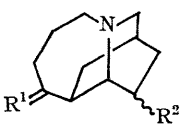


(III)



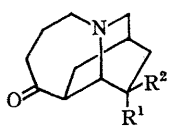
(IV a, b)

The enamine (IVa) was hydrolysed with concentrated hydrochloric acid, and the product esterified with diazomethane to afford the ketone (Va), m.p. 74°, recrystallized from n-hexane. The acetal-ester (Vb) obtained from the above ketone (Va), was converted by Corey's method into the methanesulphinyl derivative (Vc),[7] which without isolation was reduced with aluminium amalgam to (Vd), which was an oil, giving two spots on t.l.c. This oil, without purification, was subjected to the Huang-Minlon reduction, giving (Ve). Subsequent acidic hydrolysis gave the ketone (VI) as an oil, which was purified by chromatography on silica gel. Elution with ethyl acetate afforded the (VIa) as an oil, i.r. (film) 1700 cm.$^{-1}$; n.m.r. ($CDCl_3$) τ 9·08(3H, t, J 6 c./sec.); picrate, m.p. 178—180°. The other fraction eluted with ethyl acetate and successively with methyl chloride : ethanol (9 : 1) yielded (VIb) as an oil, i.r. (film) 1700 cm.$^{-1}$; n.m.r. ($CDCl_3$) τ 9·08(3H, t, J 6 c./sec.); picrate, m.p. 184—186°. The ratio of (VIa) and (VIb) was approximately 2 : 3, and each gave one spot on



(V)

	R^1	R^2
a	O	CO_2Me
b	$O[CH_2]_2O$	CO_2Me
c	$O[CH_2]_2O$	$CO{\cdot}CH_2{\cdot}SO{\cdot}Me$
d	$O[CH_2]_2O$	CO·Me
e	$O[CH_2]_2O$	Et



(VI)a; R^1=H, R^2=Et
b; R^1=Et, R^2=H

t.l.c. The R_F value of (VIa) was slightly greater than that of (VIb), suggesting that the former is the *exo*-ethyl ketone (VIa) and the latter the *endo*-ethyl derivative (VIb).

A mixture of (VIa) and phenylhydrazine in ethanol was heated at reflux for 6 hr., and to the resulting mixture was added anhydrous formic acid.[8] The whole solution was heated at 100° in a current of nitrogen for 30 min. to afford (±)-ibogamine, m.p. 132—134° (recrystallized from di-isopropyl ether) in 48% yield, identified by mixed m.p., i.r., u.v., mass spectroscopic, and t.l.c. comparison with the authentic specimen kindly supplied by Dr. W. Nagata.

On treatment of (VIb) in a similar way, (±)-epi-ibogamine (Ib), m.p. 194—196°, was obtained in 60% yield.

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