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THE TOTAL SYNTHESIS OF dl-EPIIBOGAMINE

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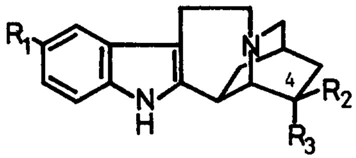
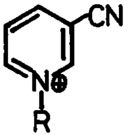
The iboga alkaloids are not only unique in chemical structures (1), but also interesting in physiological activities (2). The total syntheses of dl-ibogamine(Ia) and dl-ibogaine(Ic), the representative members of these alkaloids, and of the corresponding C-4 epimers were already achieved by Büchi (3), Nagata (4), and Sallay (5), independently. The syntheses of some derivatives having the isoquinuclidine ring system were also reported (6).

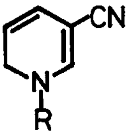
In this paper, we describe a different method of the total synthesis of dl-epiibogamine (Ib).



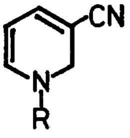
(Ia) R_1=H, R_2=Et, R_3=H
(Ib) R_1=H, R_2=H, R_3=Et
(Ic) R_1=OMe, R_2=Et, R_3=H
(Id) R_1=OMe, R_2=H, R_3=Et



(II)

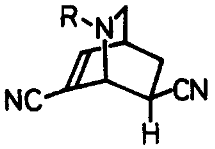


(IIIa)

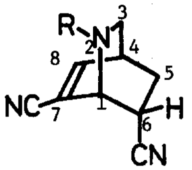


(IIIb)

R=-$(CH_2)_3$CN



(IVa)



(IVb)

N-γ-cyanopropyl-3-cyanopyridinium bromide(II)(m.p. 130-131°) obtained from 3-cyanopyridine with γ-bromobutyronitrile was reduced with sodium borohydride in aqueous sodium carbonate solution (cooling, 10-15 min.) to give a mixture of the 1,6-dihydropyridine(IIIa) and the 1,2-dihydropyridine(IIIb) as red oil[IR. ν_{max} 2240, 2195 cm^{-1}(C≡N)] (7).

When a crude mixture of the foregoing dihydropyridines(IIIa and IIIb) was condensed

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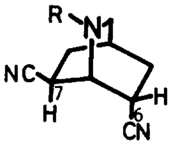
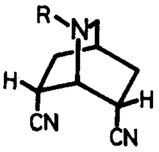
with the excess of acrylonitrile (8), the exo derivative of isoquinuclidine(IVa)[m.p. 80-81°; IR. ν_{max}2245, 2220(C≡N), 1610 cm^{-1}(C=C); NMR. τ2.65(quart. 1 vinylic H, J=8 & 2 cps), τ6.15 (t. 1H at C-1), τ6.62(quart. one H at C-3 at the opposite side to the 7,8-double bond, J=10 & 3 cps); 4.1% yield] and the endo derivative(IVb)[m.p. 83-85°; IR. ν_{max}2245, 2210(C≡N), 1610 cm^{-1}(C=C); NMR. τ2.53(quart. 1H, J=8 & 2 cps), τ6.12(quart. 1H); 10.1% yield] were obtained after purification by alumina chromatography. The endo derivative(IVb) was hydrogenated with platinum in ethyl acetate under 25-35 lb/in^2 pressure of hydrogen (Parr apparatus) to afford the di(endo-exo)-nitrile(Va) as colorless oil (picrate, m.p. 185-186°) in 67% yield and the di(endo-endo)-nitrile(Vb)(m.p. 92-93°) in 19.5% yield after separation by chromatography. Only one product, di(exo-exo)-nitrile(Vc)(m.p. 81-82°), however, was quantitatively generated on the hydrogenation of the exo-nitrile(IVa) with 10% palladium on charcoal in ethyl acetate.

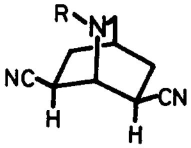


(Va)



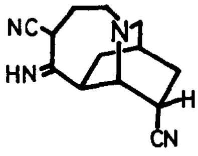
R=-(CH$_2$)$_3$CN

(Vb)

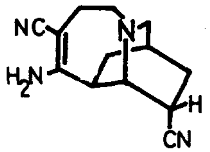


(Vc)

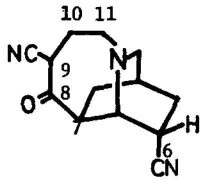
The products(Va, Vb and Vc) were respectively transformed by N-methylanilinolithium into a tautomeric mixture(VI)(m.p. 180-185°) of the imine(VIa) and enamine(VIb), and thence, by hydrolysis with acetic acid to the keto-dinitrile(VII)[m.p. 229-232°; FeCl$_3$ test, positive; IR. ν_{max}2240(C≡N), 1700 cm^{-1}(C=O)] as a sole product isolated in 20% yield from Va and Vc, but in a poor yield from Vb. Based upon the preliminary experiments with N-methylisoquinuclidine derivatives (6e), a solution of the di(endo-endo)-nitrile(Vb) in t-butanol containing a catalytic amount of potassium t-butoxide was heated at reflux for 30 min. to afford the most stable di(endo-exo)-nitrile(Va) in a quantitative yield. The finding of this conversion of Vb to Va prior to formation of the seven membered ring made the above Ziegler reaction more effective in respect of the yield than the direct cyclization of Vb to VI. The reason why only one product(VII) was obtained through VI by a Ziegler reaction from any starting material of the three(Va, Vb and Vc) could be readily understood, that is, the endo nitrile group at C-7 of Vb was epimerized to the exo side under the above reaction condition affording Va, which was cyclized to VI. The similar epimerization of the nitrile may be assumed to have occurred at C-6 of Vc, as the endo-exo isomer is most stable in this series.



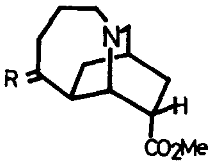
(VIa)

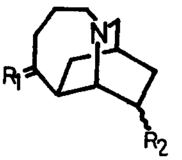


(VIb)



(VII)





(VIII) R=O
(IX) R=O-$(CH_2)_2$O

(X) R_1=O-$(CH_2)_2$-O, R_2=$COCH_3$
(XI) R_1=O-$(CH_2)_2$-O, R_2=CH_2CH_3
(XII) R_1=O, R_2=CH_2CH_3

When refluxed with concentrated hydrochloric acid in an atmosphere of nitrogen for 10 hrs., followed by esterification with diazomethane, the keto-nitrile(VII) provided the keto-ester(VIII)[m.p. 74°; IR. ν_{max} 1735(ester C=O), 1440(CH_2 of C-10), 1695 cm^{-1}(ketone C=O); NMR. τ6.25(3H, $COOC\underline{H}_3$); 73.1% yield], which was converted to the correponding ketal(IX) as an oil [IR. ν_{max} 1735(C=O), 1100 cm^{-1}(ketal C-O); NMR. τ6.05(ketal 4H),τ6.25(3H, $COOC\underline{H}_3$); 64% yield] forming the picrate(m.p. 154.5-157°). The ketal-ester(IX) was transformed by the action of methylsulfinyl carbanion (9) at a room temperature into the methylsulfinyl adduct, which without isolation, was immediately reduced with aluminum amalgam to the ketal-acetyl derivative(X) as an oil [IR. ν_{max} 1710(C=O), 1100 cm^{-1}(ketal C-O); NMR. τ6.09(ketal 4H), τ7.80(3H, $COC\underline{H}_3$)] in the yield of 27-30% yield from IX. The ethyl-ketal(XI)[colorless oil, IR.ν_{max} 1100 cm^{-1}(C-O); NMR. τ6.05(4H), τ9.03(t. 3H)] obtained from X in 64.6% yield by treatment with 100% hydrazine and potassium hydroxide in boiling ethylene glycol, was hydrolyzed with 10% hydrochloric acid to the desired ethyl-ketone(XII) as a partly crystallized substance [IR. ν_{max} 1698 cm^{-1}(C=O), NMR. τ9.03(t. 3H)].

The orientations of the substituents at C-6 of X, XI and XII are not clear on account of the possible enolization of X in the presence of a strong base during the Corey's reaction (9), but it may be assumed that the crude material consists of the endo derivative for the main part.

Finally, the phenylhydrazone of the above tricyclic ketone(XII) was submitted to the Fischer indolization refluxing with anhydrous formic acid for a half hour (10) to afford dl-epiibogamine(Ib)(m.p. 194-196°) after purification by chromatography on alumina eluted with benzene-methylene chloride(1:1). The infrared spectrum of the present product was superimposable on that of the authentic sample [lit. (3,4) m.p. 193-197°] kindly provided by Dr. W. Nagata(11). The identity of both samples was further confirmed by the mixed melting point determination, Rf values on TLC and the mass spectral comparison. Further investigation for the extension of this method is now in progress.

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7. The infrared spectra of crystallized compounds were measured in Nujol mulls, and those of the oily material were taken in film. For NMR spectra, all samples were measured in $CDCl_3$ on a Hitachi (Model H-60) Spectrometer(60 Mc), in which tetramethylsilane(10 τ) was used as internal reference. Satisfactory elemental analyses were obtained on all compounds, whose melting points are described in this paper. All synthetic substances are racemates, though each enantiomer is only delineated.
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