

THE TOTAL SYNTHESIS OF ($\pm$)-EPI-IBOGAMINE USING
THE DIELS-ALDER REACTION OF 2-PYRIDONE

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The Diels-Alder reactions of 1-methyl- and 1-benzyl-2(1H)-pyridone (I and II) with methyl acrylate (III) and acrylonitrile produced mainly the appropriate substituted isoquinuclidine derivatives which are easily accessible to iboga alkaloids. The short total synthesis of ($\pm$)-epi-ibogamine and the formal total synthesis of ($\pm$)-desethylibogamine employing the adducts were achieved as outlined below.

The adduct (IV) obtained by the Diels-Alder reaction (17% yield) of II with III was reduced with LiAlH_4 to give the methylol (V) in 80% yield. Tosylation (94%) and Grignard reaction (72%) gave the isoquinuclidine (VIa). Treatment of VIa with 2-(3-indolyl)ethyl bromide (90%) and subsequent debenzylation with $\text{C}_3\text{H}_7\text{SLi}$ (33%) afforded the indolylethylisoquinuclidine (VIIa). Cyclization to ($\pm$)-epi-ibogamine was performed by the reaction of VIIa with $(\text{MeCN})_2\text{PdCl}_2$, AgBF_4 , and Et_3N , followed by NaBH_4 reduction in 20% yield. The formal total synthesis of ($\pm$)-desethylibogamine was accomplished using the dicarboxylic acid (VIII) (41%) prepared by hydrolysis of the Diels-Alder adduct of II and maleic anhydride. Catalytic reduction (99%) of VIII and subsequent decarboxylation with $\text{Pb}(\text{OAc})_4$ (43%) gave the olefin (IX). The isoquinuclidine (VIb) obtained by reduction (90%) of IX was converted by the above-mentioned sequences into the indolylethylisoquinuclidine (VIIb) (3.7% from VIb), which had already been transformed into ($\pm$)-desethylibogamine by Trost and Genêt.

