

## SYNTHESIS OF IPALBIDINE\*

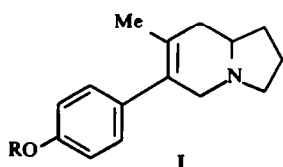
T. R. GOVINDACHARI, A. R. SIDHAYE and N. VISWANATHAN

CIBA Research Centre, Goregaon, Bombay 63, India

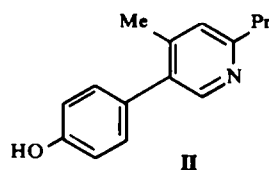
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**Abstract**—The synthesis of ipalbidine (Ia) is reported.

GOURLY *et al.*<sup>1</sup> recently reported the isolation of two indolizidine alkaloids, ipalbidine (Ia) and its glucoside ipalbine (Ib) from *Ipomoea alba* L. (Family: *Convolvulaceae*). The structure of ipalbidine was assigned on the basis of its spectral properties and dehydrogenation to 5-*p*-hydroxyphenyl-4-methyl-2-*n*-propylpyridine (II).



a: R = H  
b: R =  $\beta$ -D-glucosyl  
c: R = Me



We wish to report the synthesis of ipalbidine by a method used recently for the synthesis of the diarylindolizidine alkaloid septicine.<sup>2</sup>

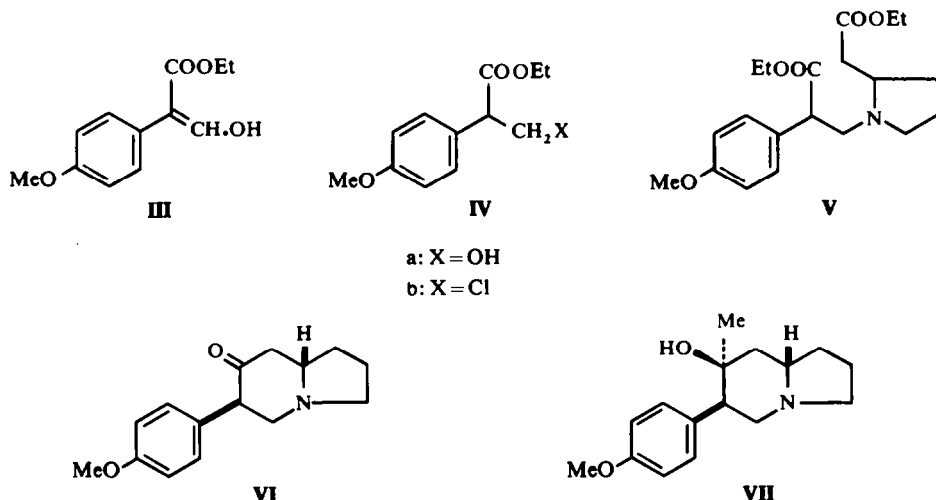
Ethyl 4-methoxyphenyl acetate, on treatment with sodium and ethyl formate, gave the hydroxymethylene derivative (III) which was reduced with sodium borohydride to the hydroxyester (IVa). This was converted to the chloride (IVb) and then condensed with ethyl 2-pyrrolidinyl acetate to yield the diester (V). Dieckmann cyclization of this followed by hydrolysis and decarboxylation gave the ketone (VI). Treatment of this with methyllithium yielded the carbinol (VII) which was dehydrated with sulphuric acid to O-methylipalbidine (Ic). Demethylation of the methyl ether with aluminium bromide gave *dl*-ipalbidine characterized as the hydrochloride, m.p. 104°. The IR spectra of the synthetic hydrochloride and the natural sample were identical. The bases regenerated from the two samples had identical TLC, IR and NMR spectra.

### EXPERIMENTAL

M.p.s are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 421 instrument.

*Ethyl  $\alpha$ -hydroxymethylene-4-methoxyphenyl acetate* (III). Na (2.5 g) was added in small lots to a stirred ice-cooled soln of ethyl 4-methoxyphenyl acetate (15 g) in dry ether (150 ml). After  $\frac{1}{2}$  hr,

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ethyl formate (10 g) was added dropwise and the mixture was stirred overnight at room temp. It was then poured on ice, the aqueous layer separated, acidified quickly and extracted with ether to give a viscous brownish oil (16 g) which gave a deep purple colour with  $\text{FeCl}_3$ . It was used as such for reduction.

*Ethyl 3-hydroxy-2-(4'-methoxyphenyl) propionate* (IVa).  $\text{NaBH}_4$  (2.5 g) was added slowly over  $\frac{1}{2}$  hr to a soln of the above hydroxymethylene ester (16 g) in MeOH (60 ml) at  $5-10^\circ$ . After stirring for 1 hr at  $10^\circ$ , water was added and the mixture extracted with  $\text{CHCl}_3$ . Chromatography of the product over silica gel in  $\text{CHCl}_3$  yielded the hydroxymethyl ester (13 g) as a viscous liquid. For analysis a sample was sublimed at  $140^\circ/0.2$  mm. (Found: C, 64.19; H, 7.42.  $\text{C}_{12}\text{H}_{16}\text{O}_4$  requires: C, 64.27; H, 7.19%).

*Ethyl 3-chloro-2-(4'-methoxyphenyl) propionate* (IVb). A soln of the above ester (18 g) in benzene (120 ml) was refluxed for 2 hr with  $\text{SOCl}_2$  (15 ml). Removal of excess  $\text{SOCl}_2$  and solvent followed by chromatography of the residue over silica gel in benzene gave the chloride (9 g) as a light yellow oil. For analysis, a sample was sublimed at  $140^\circ/0.3$  mm. (Found: C, 59.60; H, 6.46.  $\text{C}_{12}\text{H}_{15}\text{O}_3\text{Cl}$  requires: C, 59.38; H, 6.23%). The chloride was found to decompose appreciably during distillation and was used as such without distillation for the next reaction.

*Ethyl 1-(2-carbethoxy-2-(4'-methoxyphenylethyl) pyrrolidinyl)-2-acetate* (V). A soln of the above chloride (9 g) in toluene (90 ml) was refluxed with stirring with ethyl 2-pyrrolidinyl acetate<sup>3</sup> (6 g) and anhyd  $\text{K}_2\text{CO}_3$  (15 g) under  $\text{N}_2$  for 20 hr. The soln was filtered, the residue washed well with benzene and the combined filtrate evaporated *in vacuo*. The residual oil was taken up in ether, extracted with 2N HCl and the acid soln basified with ammonia and re-extracted with  $\text{CH}_2\text{Cl}_2$  to yield a brownish oil. This was chromatographed in  $\text{C}_6\text{H}_6\text{-CHCl}_3$  (1:1) over silica gel to yield the diester (2.5 g) as a light brown liquid,  $\nu_{\text{max}}$  (thin film)  $1720\text{ cm}^{-1}$ . For analysis, the ester was sublimed at  $140^\circ/10^{-3}$  mm. (Found: C, 65.74; H, 7.84.  $\text{C}_{20}\text{H}_{26}\text{NO}_6$  requires: C, 66.09; H, 8.04%). For the subsequent reaction, the ester which was homogenous by TLC was used as such without distillation.

*6-(4'-Methoxyphenyl)-7-oxoindolizidine* (VI). Potassium (2.6 g) and ferric nitrate (50 mg) were added to anhyd liquid ammonia (60 ml) and the soln stirred for  $\frac{1}{2}$  hr under  $\text{N}_2$ . A soln of triphenylmethane (16 g) in ether (100 ml) was then added and the deep red soln stirred for 1 hr at room temp and then refluxed for 1 hr more. The soln was cooled and a soln of the above diester (7 g) in dry THF (50 ml) was added. The resulting soln was refluxed for 1 hr, then left overnight at room temp and decomposed with 2N HCl (150 ml). The acid soln was separated, extracted with ether to remove non-basic material and then refluxed under  $\text{N}_2$  for 4 hr. The acid soln was cooled, basified with ammonia and extracted with  $\text{CH}_2\text{Cl}_2$  to yield a dark brown oil. Chromatography of this over silica gel in  $\text{C}_6\text{H}_6\text{-CHCl}_3$  (1:1) yielded the ketoindolizidine (2 g),  $\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2}$   $1710\text{ cm}^{-1}$ . It crystallized from ether-hexane as colourless needles, m.p.  $105-106^\circ$ . (Found: C, 73.24; H, 8.00.  $\text{C}_{15}\text{H}_{19}\text{NO}_2$  requires: C, 73.44; H, 7.81%).

*7-Hydroxy-6-(4'-methoxyphenyl)-7-methylindolizidine* (VII). MeI (20 g) was added to a suspension of Li

(2.25 g) in ether (80 ml) and the soln refluxed with stirring under  $N_2$  for  $1\frac{1}{2}$  hr. The soln was cooled and a soln of the above ketone (2.5 g) in dry THF (10 ml) was added. The soln was refluxed for 8 hr, cooled and decomposed with 2N HCl. The acid soln was separated, basified with ammonia and extracted with  $CH_2Cl_2$ . Chromatography of the product over alumina in  $C_6H_6$ -MeOH (1%) yielded the hydroxy-indolizidine (1.5 g), needles (from ether-hexane), m.p. 133–135°,  $\nu_{max}^{CH_2Cl_2}$ : 3580  $cm^{-1}$ . (Found: C, 73.26; H, 8.70.  $C_{16}H_{23}NO_2$  requires: C, 73.53; H, 8.87%).

6-(4'-methoxyphenyl)-7-methyl- $\Delta^{6,7}$ -dehydroindolizidine (Ic). The above hydroxyindolizidine (1.2 g) was heated with conc  $H_2SO_4$  (10 ml) and water (8 ml) at 80° for 45 min under  $N_2$ . The reddish soln was poured on ice, basified with ammonia and extracted with  $CH_2Cl_2$ . Chromatography of the product over alumina in  $C_6H_6$  yielded the dehydroindolizidine (0.7 g) characterized as the hydrochloride, m.p. 215–217° from MeOH-ether. (Found: C, 68.86; H, 8.04.  $C_{16}H_{21}NO \cdot HCl$  requires: C, 68.86; H, 7.93%). The NMR spectrum ( $CDCl_3$ ) of the base regenerated from the hydrochloride showed the aromatic protons (4H) as an AB quartet at  $\delta$  6.68–7.18, one OMe at  $\delta$  3.7 and the vinylic C—CH<sub>3</sub> at  $\delta$  1.57 ppm. The rest of the protons appeared as broad signals at  $\delta$  1.65–3.5 ppm.

6-(4'-Hydroxyphenyl)-7-methyl- $\Delta^{6,7}$ -dehydroindolizidine (dl-Ipalbidine) (Ia). A soln of the foregoing dehydroindolizidine (2.1 g) in dry  $CS_2$  (80 ml) was stirred for 36 hr at 30° with anhyd  $AlBr_3$  (8 g). The soln was evaporated *in vacuo* and decomposed with HCl. The acid soln was basified with ammonia and extracted with  $CH_2Cl_2$ . Chromatography of the product over silica gel in  $CHCl_3$  yielded dl-ipalbidine, characterized as the hydrochloride, m.p. 104° from MeOH-ether. (Found: C, 64.05; H, 7.97.  $C_{15}H_{20}NOCl \cdot H_2O$  requires: C, 63.48; H, 7.81%). The IR spectra of the synthetic hydrochloride and the natural sample were identical. The bases regenerated from the two samples had identical TLC, IR and NMR spectra.

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