

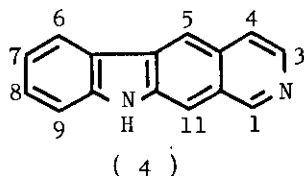
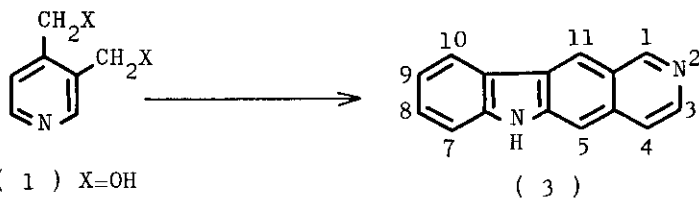
## A FASCINATING SYNTHESIS OF OLIVACINE

Tetsuji Kametani,\* Yoshifumi Ichikawa, Toshio Suzuki, and Keiichiro Fukumoto  
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

The tumour-inhibiting alkaloid olivacine (11) has been synthesised by a reaction of indole with 4-(1-bromoethyl)-3-bromomethyl-2-methylpyridine (10).

The indole alkaloid olivacine (11)<sup>2</sup> has much interest from the pharmacological<sup>2</sup> and biogenetic<sup>3</sup> points of view, and the total syntheses of olivacine and the similar alkaloid ellipticine have been reported by many groups.<sup>4</sup> We have investigated a simple synthesis of olivacine (11) and here wish to report one-step synthesis of 11 from indole.

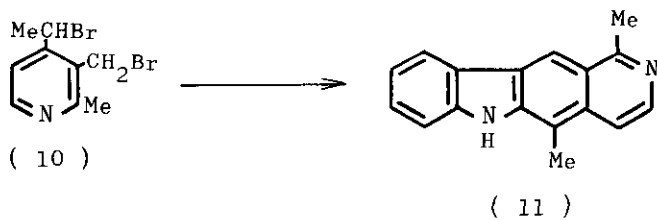
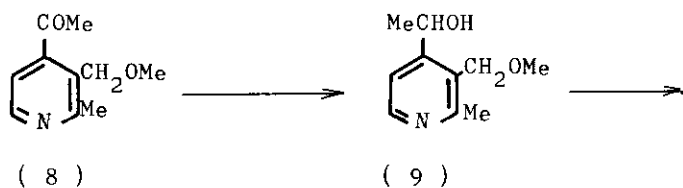
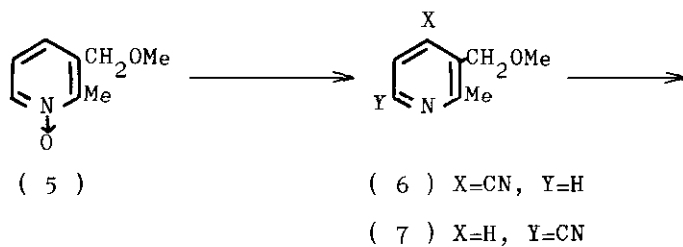
Firstly, we examined the regioselectivity of the reaction of indole with 3,4-dibromomethylpyridine (2) hydrobromide. Refluxing 3,4-dihydroxymethylpyridine (1)<sup>5</sup> in 48 % hydrobromic acid for 1 hr gave 3,4-dibromomethylpyridine (2) hydrobromide, which was, without purification, treated with indole in boiling dimethylformamide for 10 min to afford only the dehydrogenated 6H-pyrido[4,3-b]carbazole (3), m.p. 284 - 286° (lit.,<sup>5</sup> 285 - 286°), in 15 % yield. The u.v. spectrum was identical with that of an authentic sample, but different from that of 10H-pyrido[4,3-b]carbazole (4).<sup>6</sup> Thus we found this reaction proceeded regioselectively to form an olivacine-type compound. With this finding in hand, we tried a synthesis of olivacine by this method.



Cyanation of 3-methoxymethyl-2-methylpyridine-1-oxide (5)<sup>7</sup> with potassium cyanide in the presence of dimethyl sulphate gave a mixture of the 4-cyano-compound (6), in 20 % yield, m.p. 43.5 - 44.5° [ $\nu_{\max}$  (CHCl<sub>3</sub>) 2225 cm<sup>-1</sup>,  $\delta$  (CDCl<sub>3</sub>) 7.27 (d,  $J$  5 Hz, C<sub>5</sub>-H), 8.48 (d,  $J$  5 Hz, C<sub>6</sub>-H)] and the 6-cyano-isomer (7) in 30 % yield, m.p. 64.5 - 65.5° [ $\nu_{\max}$  (CHCl<sub>3</sub>) 2235 cm<sup>-1</sup>,  $\delta$  (CDCl<sub>3</sub>) 7.30 and 7.62 (each d,  $J$  8 Hz, C<sub>5</sub>-H and C<sub>4</sub>-H)], which were easily separated by silica gel chromatography. Grignard reaction of 6 with methylmagnesium bromide in ether afforded 4-acetylpyridine (8), b.p. 77 - 79° (4 mm Hg), in 60.5 % yield [ $\nu_{\max}$  (CHCl<sub>3</sub>) 1700 cm<sup>-1</sup>,  $\delta$  (CDCl<sub>3</sub>) 2.36 (3H, s, COMe)], which was reduced with sodium borohydride in methanol to furnish 4-(1-hydroxyethyl)-3-methoxymethyl-2-methylpyridine (9) in quantitative yield, m.p. 101 - 102° [ $\delta$  (CDCl<sub>3</sub>) 1.26 (3H, d,  $J$  6 Hz, CH<sub>3</sub>CHOH) and 4.88 (1H, q,  $J$  6 Hz, CH<sub>2</sub>CHOH)].

Refluxing this alcohol (9) in 47 % hydrobromic acid for 1.5 hr gave the corresponding dibromide (10), which was, without isolation and purification, condensed with indole by heating to afford olivacine (11), m/e 246 (M<sup>+</sup>), m.p. >300°, (lit.,<sup>8</sup> m.p. 318 - 324°) as yellow needles in 30 % yield after purification by silica gel chromatography and recrystallisation from methanol. The u.v.<sup>8</sup> [ $\lambda_{\max}$  (MeOH)

375, 329, 314, 292, 287, 276, and 238] and i.r. spectra<sup>9</sup> of this product were identical with those of authentic sample.



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