A FASCINATING SYNTHESIS OF OLIVACINE

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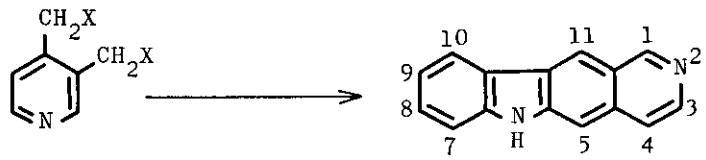
The tumour-inhibiting alkaloid olivacine (11) has been synthesised by a reaction of indole with 4-(1-bromoethyl)-3-bromomethyl-2-methylpyridine (10).

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

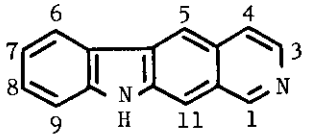
Firstly, we examined the regioselectivity of the reaction of indole with 3,4-dibromomethylpyridine (2) hydrobromide. Refluxing 3,4-dihydroxymethylpyridine (1)[5] in 48 % hydrobromic acid for 1 hr gave 3,4-dibromomethylpyridine (2) hydrobromide, which was, without purification, treated with indole in boiling dimethylformamide for 10 min to afford only the dehydrogenated 6H-pyrido[4,3-b]carbazole (3), m.p. 284 - 286° (lit.,[5] 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).[6] 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.



(1) X=OH

(2) X=Br

(3)

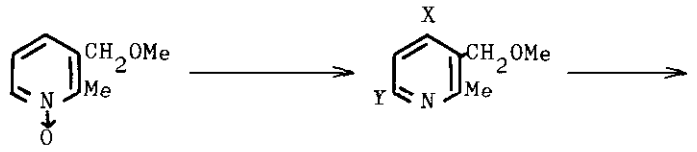


(4)

Cyanation of 3-methoxymethyl-2-methylpyridine-1-oxide (5)[7] 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° [ν_{max} ($CHCl_3$) 2225 cm^{-1}, δ ($CDCl_3$) 7.27 (d, J 5 Hz, C_5 - H), 8.48 (d, J 5 Hz, C_6 - H)] and the 6-cyano-isomer (7) in 30 % yield, m.p. 64.5 - 65.5° [ν_{max} ($CHCl_3$) 2235 cm^{-1}, δ($CDCl_3$) 7.30 and 7.62 (each d, J 8 Hz, C_5 - H and C_4 - 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 [ν_{max} ($CHCl_3$) 1700 cm^{-1}, δ ($CDCl_3$) 2.36 (3H, s, COMe)], which was reduced with sodium borohydride in methanol to furnish 4-(1-hydroxyethyl)-3-methoxy-methyl-2-methylpyridine (9) in quantitative yield, m.p. 101 - 102° [δ ($CDCl_3$) 1.26 (3H, d, J 6 Hz, CH_3CHOH) and 4.88 (1H, q, J 6 Hz, CH_3CHOH)].

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^+), m.p. >300°, (lit.,[8] m.p. 318 - 324°) as yellow needles in 30 % yield after purification by silica gel chromatography and recrystallisation from methanol. The u.v.[8] [λ_{max} (MeOH)

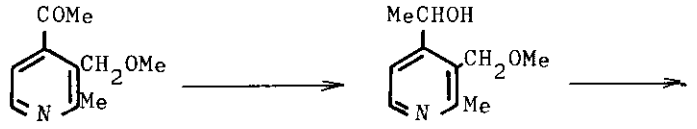
375, 329, 314, 292, 287, 276, and 238] and i.r. spectra[9] of this product were identical with those of authentic sample.



(5)

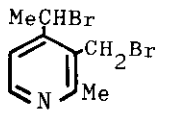
(6) X=CN, Y=H

(7) X=H, Y=CN

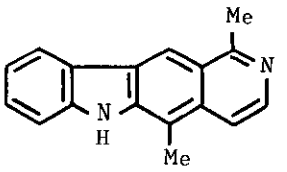


(8)

(9)



(10)



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REFERENCES

1 B. Gilbert, "The Alkaloids", Vol. XI, ed. by R. H. F. Manske, Academic Press, New York, 1968, p. 279.

2 G. H. Svoboda, G. A. Poore, and M. L. Montfort, J. Pharm. Sci., 1968, 57, 1720.

3 E. Wenkert, J. Amer. Chem. Soc., 1962, 84, 98.

4 J. P. Kutney and D. S. Grierson, Heterocycles, 1975, 3, 171, and refs. cited herein.

5 F. Le. Goffic, A. Gouyette, and A. Ahond, Tetrahedron, 1973, 29, 3357.

6 T. Kametani, Y. Ichikawa, T. Suzuki, and K. Fukumoto, Heterocycles, 1974, 2, 171; Tetrahedron, 1974, 30, 3713.

7 Y. Sato, Chem. and Pharm. Bull. (Japan), 1958, 6, 222.

8 J. Schmutz and F. Junziker, Pharm. Acta Helv., 1958, 33, 341.

9 J. Schmutz and H. Wittmer, Helv. Chim. Acta, 1960, 43, 798.

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