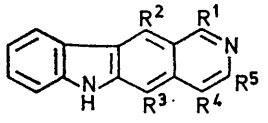
# Studies on the Syntheses of Heterocyclic Compounds. Part CDXXXIV.† A Novel Total Synthesis of Olivacine (1,5-Dimethyl-6*H*-pyrido[4,3-*b*]-carbazole)

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

The tumour-inhibiting alkaloid olivacine (1) has been synthesised in one step by heating indole and 4-(1-hydroxyethyl)-3-methoxymethyl-2-methylpyridine (14) in 47% hydrobromic acid.

THE alkaloid olivacine (1), isolated from *Aspidosperma olivaceum* Müll. Arg.,[1] *A. longepetiolatum* Kuhlm.,[2] *A. australe* Müll. Arg.,[3] and *Tabernaemontana psychotrifolia*,[4] has stimulated much interest because of its antitumour and antileukaemic activity.[5] Although several syntheses have been described, these are very lengthy.[5-7] A one-step synthesis of pyridocarbazoles from an indole and a pyridine derivative was sought, since indole itself is expensive and choice of an appropriate pyridine derivative would permit access to many derivatives of olivacine and of ellipticine.



(1) $R^1 = R^3 = Me, R^2 = R^4 = R^5 = H$
(2) $R^1 = R^4 = R^5 = H, R^2 = R^3 = Me$
(3) $R^1 = R^2 = R^3 = H, R^4 = OAc, R^5 = Me$
(4) $R^1 = R^2 = R^3 = R^4 = R^5 = H$

We have previously reported [8] a reaction of indole with 4,5-bisbromomethyl-3-hydroxy-2-methylpyridine hydrobromide (5) to give dihydropyridocarbazole derivatives (6) and (7); these were easily converted into pyridocarbazole derivatives (3) and (8), closely similar to the natural alkaloids. However, compound (6), required for conversion into olivacine (1) and ellipticine (2) derivatives, was obtained as a minor product. At this stage, we supposed this type of reaction to proceed stepwise *via* an ionic intermediate and, in fact, succeeded in an alternative stepwise synthesis of the pyridocarbazole derivatives (3) and (8).[9] We now report a new synthesis of olivacine (1) by a modification of the above methods.

We first tried to synthesise the model compound 6*H*-pyrido[4,3-*b*]carbazole (4).[10,11] Refluxing 3,4-bishydroxymethylpyridine (9) [12] in 47% hydrobromic acid gave 3,4-bisbromomethylpyridine hydrobromide, which, without purification, was treated with indole in boiling

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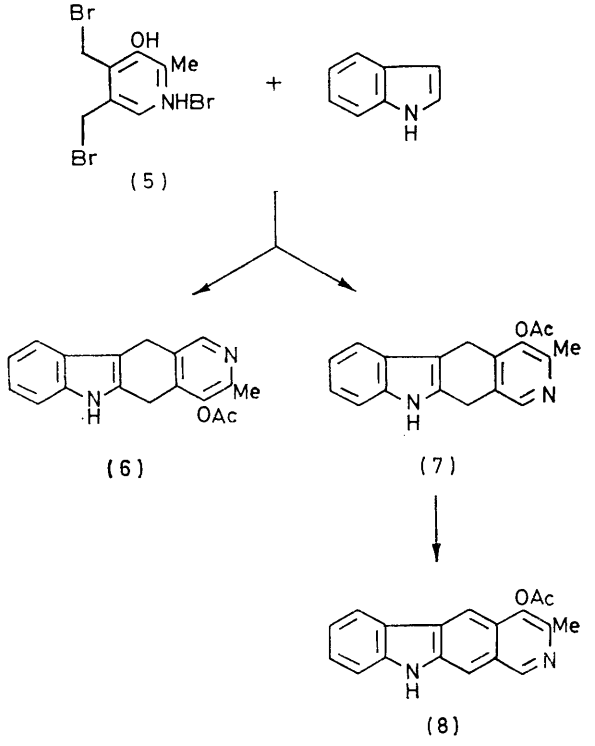
dimethylformamide to afford the expected olivacine-type compound (4) as the only product.

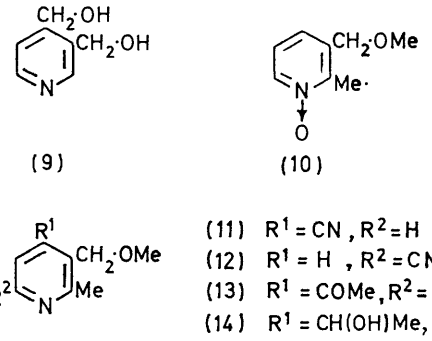
In the light of the above result, we attempted a one-step synthesis of olivacine from 4-(1-hydroxyethyl)-3-methoxymethyl-2-methylpyridine (14) and indole. Treatment of 3-methoxymethyl-2-methylpyridine 1-oxide (10) [13] with potassium cyanide in the presence of dimethyl sulphate gave a mixture of the desired product (11) and its structural isomer (12), which were easily separated by chromatography. The i.r. spectra ($CHCl_3$) of both (11) and (12) showed cyano-absorption, as a weak band at 2 225 $cm^{-1}$ and a very strong band at 2 235 $cm^{-1}$, respectively. The n.m.r. spectrum of compound (11) lacked a signal due to the γ-proton, whereas that of (12) lacked an α-proton signal. *ortho*-Coupling was observed in both cases.

A Grignard reaction of (11) with methylmagnesium iodide, followed by hydrolysis with 6N-hydrochloric acid gave 4-acetyl-3-methoxymethyl-2-methylpyridine (13) [$\nu_{max.}$ ($CHCl_3$) 1 700 $cm^{-1}$ (CO), δ ($CDCl_3$) 2.36 (COMe)], which was reduced with sodium borohydride in methanol to afford 4-(1-hydroxyethyl)-3-methoxymethyl-2-methylpyridine (14) [δ ($CDCl_3$) 1.26 (3 H, d, *J* 6 Hz, $CH_3$·CH·OH) and 4.88 (1 H, q, *J* 6 Hz, $CH_3$·CH·OH)].

Refluxing the alcohol (14) in 47% hydrobromic acid for 1.5 h gave the corresponding dibromide, which, without isolation, was condensed with indole by heating




olivacine (1) in low yield after silica gel chromatography. Natural olivacine was not available for direct comparison, but the u.v., i.r. and mass spectral data of the synthetic olivacine (1) were identical with those published.[1-3,14]




## EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro-apparatus (MP-S2). I.r. spectra were measured with a Hitachi EPI-3 spectrophotometer, u.v. spectra were taken for solutions in methanol with a Hitachi EPS-3 recording spectrophotometer. Mass spectra were measured with a Hitachi RMU-7 spectrometer. N.m.r. spectra were measured for solutions in deuteriochloroform (tetramethylsilane as internal standard) with JNM-PMX 60 and Hitachi H-60 instruments.

6H-*Pyrido*[4,3-b]*carbazole* (4).—A mixture of 3,4-bis-hydroxymethylpyridine (9) (2.48 g) and 47% hydrobromic acid (10 ml) was refluxed for 1 h, then evaporated under reduced pressure. The residue was mixed with indole (1.3 g) and dimethylformamide (35 ml), and the mixture was refluxed for 10 min at 170—180 °C. Removal of the solvent left a residue which was purified by chromatography on silica gel (50 g). Elution with benzene–methanol (99 : 1 v/v) afforded 6*H*-pyrido[4,3-*b*]carbazole (4) (35 mg) as yellow needles, m.p. 284—286° (from acetone) (lit.,[10] 285—296°; lit.,[11] 286—289°).

5-*Methoxymethyl*-6-*methylpyridine*-2-*carbonitrile* (12) *and* 3-*Methoxymethyl*-2-*methylpyridine*-4-*carbonitrile* (11).—To a solution of 3-methoxymethyl-2-methylpyridine 1-oxide (2 g) in dry benzene (50 ml) was added slowly a solution of dimethyl sulphate (2 ml) in dry benzene (20 ml). The mixture was stirred for 15 h at room temperature and the oil which separated was collected by decantation. The organic layer was extracted with water. The oil and the aqueous extract were combined and diluted with ethanol (20 ml). To this solution was added in small portions potassium cyanide (2 g) in water (10 ml) with stirring at 20—25 °C. The resulting solution was stirred for an additional 3 h at the same temperature. The mixture was extracted with chloroform, and the extract was washed with saturated aqueous sodium chloride, dried ($K_2CO_3$), and evaporated. The residue was chromatographed on silica gel (40 g). Elution with benzene afforded the 2-*carbonitrile* (12) (620 mg) as needles, m.p. 64.5—65.5° (from n-hexane) (Found: C, 66.9; H, 6.25; N, 17.15. $C_9H_{10}N_2O$ requires C, 66.65; H, 6.2; N, 17.25%), $\nu_{max.}$ ($CHCl_3$) 2 235 (CN) and 1 080 $cm^{-1}$ ($OCH_3$), δ($CCl_4$) 2.34 (3 H, s, $CH_3$), 3.32 (3 H, s, $OCH_3$), 4.30 (2 H, s, $CH_2$·$OCH_3$), 7.30 (1 H, d, *J* 8 Hz, 3-H), and 7.63 (1 H, d, *J* 8 Hz, 4-H).

Elution with benzene–methanol (99.5 : 0.5 v/v) afforded the 4-*carbonitrile* (11) (405 mg) as needles, m.p. 43.5—44.5° (from n-hexane) (Found: C, 66.3; H, 6.2%), $\nu_{max.}$ ($CHCl_3$) 2 225 (CN) and 1 080 $cm^{-1}$ ($OCH_3$), δ($CCl_4$) 2.63 (3H, s, $CH_3$),

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3.40 (3 H, s, $OCH_3$), 4.58 (2 H, s, $CH_2$·$OCH_3$), 7.27 (1 H, d, *J* 5 Hz, 5-H), and 8.48 (1 H d, *J* 5 Hz, 6-H).

4-*Acetyl*-3-*methoxymethyl*-2-*methylpyridine* (13)—To a cooled solution of methylmagnesium iodide in ether [from methyl iodide (2.5 g) and magnesium (400 mg)] was added dropwise a solution of (11) (300 mg) in ether (70 ml) with stirring, and the mixture was refluxed for 12 h. After cooling to 0 °C, 6N-hydrochloric acid (10 ml) was added slowly, and the mixture was refluxed for 3 h. The solvent was distilled off and the residue was basified with concentrated ammonia and extracted with chloroform. The extract was washed with saturated aqueous sodium chloride, dried ($K_2CO_3$), and evaporated. The residue was purified by chromatography on silica gel (6 g). Elution with chloroform gave the 4-*acetylpyridine* (13) as an oil (220 mg), b.p. 77—79° at 4 mmHg (Found: C, 67.0; H, 7.75; N, 8.2. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%), $\nu_{max.}$ ($CHCl_3$) 1 700 (CO) and 1 090 $cm^{-1}$ ($OCH_3$), $\delta$($CCl_4$) 2.36 (3 H, s, $COCH_3$), 2.49 (3 H, s, $CH_3$), 3.29 (3 H, s, $OCH_3$), 4.40 (2 H, s, $CH_2$·$OCH_3$), 6.90 (1 H, d, *J* 5 Hz, 5-H), and 8.31 (1 H, d, *J* 5 Hz, 6-H).

4-(1-*Hydroxyethyl*)-3-*methoxymethyl*-2-*methylpyridine* (14).—To a stirred solution of (13) (60 mg) in methanol (10 ml) was added sodium borohydride (60 mg), and the mixture was refluxed for 1 h. The solvent was removed and the residue was decomposed with water and then extracted with chloroform. The extract was washed with water, dried ($K_2CO_3$), and evaporated to give the 4-(1-*hydroxyethyl*)*pyridine* (14) (60 mg) as prisms, m.p. 101—102° (from benzene) (Found: C, 66.5; H, 8.2; N, 7.9. $C_{10}H_{15}NO_2$ requires C, 66.25; H, 8.35; N, 7.75%), $\nu_{max.}$ ($CHCl_3$) 1 080 $cm^{-1}$ ($OCH_3$), $\delta$($CDCl_3$) 1.26 (3 H, d, *J* 6 Hz, CHOH·$CH_3$), 2.37 (3 H, s, $CH_3$), 3.22 (3 H, s, $OCH_3$), 4.30 (2 H, s, $OCH_2$·$OCH_3$), and 4.88 (1 H, q, *J* 6 Hz, $CH_3$·CHOH).

*Olivacine* (1).—A mixture of compound (14) (60 mg) and 47% hydrobromic acid (2 ml) was refluxed for 1.5 h, and then indole (80 mg) was added. The mixture was refluxed for an additional 5 h, cooled, basified with 10% ammonia, and extracted with chloroform. The extract was washed with saturated aqueous sodium chloride, dried ($K_2CO_3$), and evaporated, and the residue was chromatographed on silica gel (5 g). Elution with chloroform–methanol (99 : 1 v/v) afforded olivacine (1) (5 mg) as yellow needles, m.p. >300° (from methanol) (lit.,[1] 318—324°), $M^+$ 246, with u.v. [$\lambda_{max.}$ (MeOH) 374, 328, 313sh, 293, 287, 276, and 238 nm]. and i.r. (KBr)[14] spectra identical with those reported.

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