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STUDIES ON INDIAN MEDICINAL PLANTS : PART 91[1] - STRUCTURE AND SYNTHESIS OF ALAMARIDINE, A NOVEL 5-METHYLBENZOPYRIDOQUINOLIZINE ALKALOID FROM ALANGIUM LAMARCKII

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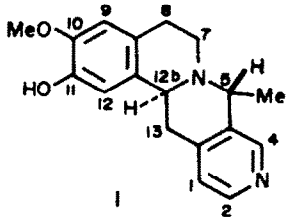
Abstract : The structure of alamaridine (1), a novel benzopyridoquinolizine alkaloid, was established by spectral data. However, its stereochemistry could only be determined now by a total synthesis involving the key cyclisation of an 1-methyl-2-pyridylmethyl-3,4-dihydroisoquinolinium salt 19a in presence of pivaloyl chloride and triethylamine. O-Benzyldehydroalamaridine thus formed was reduced by sodium cyanoborohydride and then deprotected to obtain alamaridine (1) and 5-epi-alamaridine (26). Isoalamaridine (27) and its 5-epimer (28) were also synthesised following the same route.

We earlier reported[2,3] a number of alkaloids with the novel benzopyridoquinolizine skeleton from the seeds of Alangium lamarckii Thw. (N.O. Alangiaceae). Herein we describe in detail the isolation, structure elucidation and total synthesis of alamaridine (1), one more biogenetically fascinating congener of the same class, a preliminary account of which has already been published[4,5]. The syntheses of 5-epi-alamaridine, isoalamaridine and its 5-epimer still to be encountered in nature are also presented.



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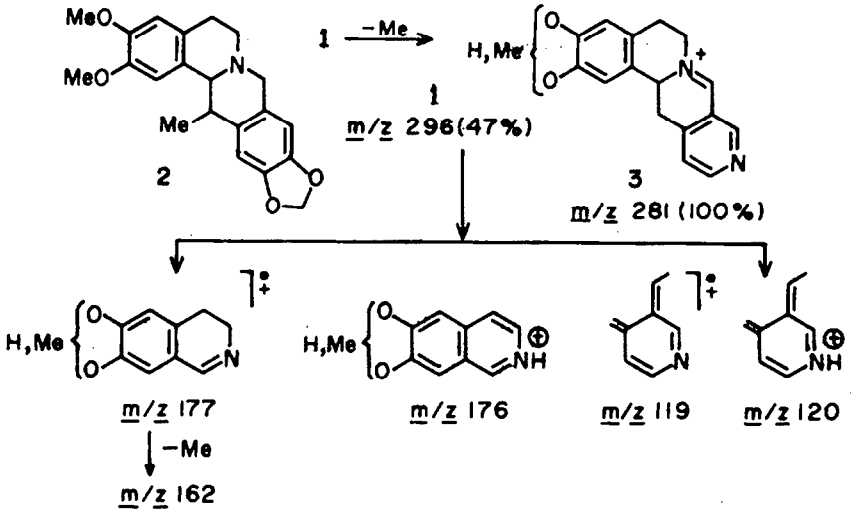
Alamaridine, m.p.196°C was obtained in ca 0.0001% yield from the weakly basic fraction of the methanolic extract of A. lamarckii seeds. The optical rotation of the compound could not be ascertained due to paucity of material. Its uv maxima at 258 and 286 nm (300 nm in alkaline medium) were compatible with the presence of a pyridine and hydroxytetrahydroisoquinoline moieties in 1.

The ^{1}H NMR spectrum of the compound exhibited signals for one secondary methyl (δ 1.42) and three singlets due to one OMe (δ 3.90) and two aromatic protons (δ 6.66 and 6.84) of the 6,7-disubstituted tetrahydroisoquinoline, while a singlet at δ 8.44 and two doublets at δ 8.40 and 7.08 suggested 3,4-disubstituted pyridine moiety.

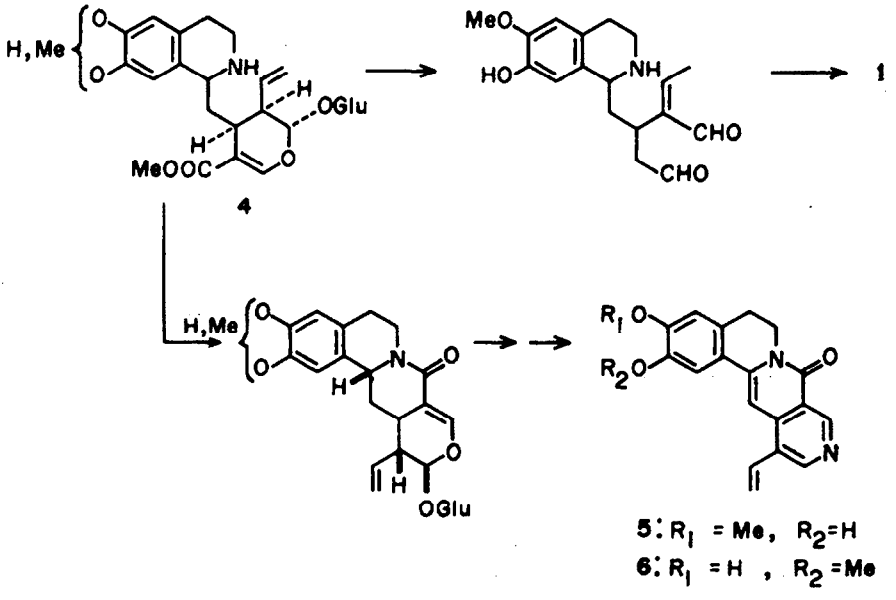
The mass spectrum of alamaridine displayed peaks at m/z 177, 176 and 162, characteristic of a tetrahydroisoquinoline bearing an OH and one OMe group in the phenyl ring and two peaks at m/z 120 and 119 conceivably derived from the pyridine moiety (**Scheme 1**). The most noteworthy feature, was the base peak for the M-Me fragment. The unsually high intensity of the peak not only indicated the facile loss of the secondary methyl (unlike the expulsion of methyl from an OMe group in the case of other closely related benzopyridoquinolizine alkaloids[3]) but also the location of the same function at C-5 rather than at the more usual C-13 position. Because, in 13-methyltetrahydroprotoberberines (eg. 2) the cleavage of C-ring

predominates over the loss of the methyl substituent (rel. int. 12%) and the base peak is derived from either of the retro Diels-Alder fragments[6,7]. Evidently, the expulsion of C-5 methyl group in 1 leads to the stable iminium ion 3 (**Scheme 1**).

The gross structure of alamaridine thus envisaged could also be rationalised biogenetically invoking amination of an intermediate derived from the glycoside 4 (**Scheme 2**), a precursor also postulated for its benzopyridoquinolizine congeners like alangimarine (5) and isoalangimarine (6)[3]. The relative positions of the OMe and OH groups in 1 at C-10 and C-11 respectively could be arrived at from the uv spectra of its iodine oxidation product in neutral, acidic and alkaline (partial shift of the 368 nm band to 408 nm) solution which were more akin to those of alangimarine (5) than of isoalangimarine (6). The relative stereochemistry of 1 at C-5 and C-12b could, however, be established only by its total synthesis as described in the sequel.



Scheme 1

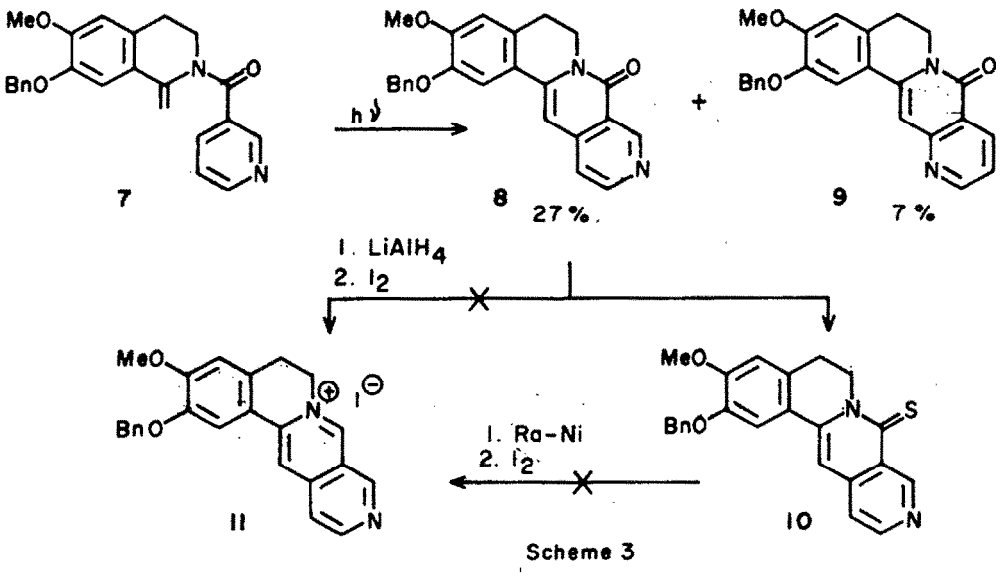


Scheme 2

The crux of the problem was to introduce a methyl function at C-5 in a benzopyridoquinolizine skeleton. We initially sought direct insertion of the methyl group to a benzopyridoquinolizinium ion such as 11 (cf synthesis[8] of 8-alkyltetrahydroprotoberberine) and subsequent reduction of the product to obtain the target compound. However, our attempts to prepare the salt 11 by reduction of the lactam 8[9] or the thiolactam 10 and subsequent iodine oxidation were unsuccessful (**Scheme 3**).

We, therefore, took recourse to cyclisation of an intermediate such as 12 with a built-in C-5 methyl to construct the alamaridine skeleton 13 analogous to the recently reported[10] photocyclisation of N-benzylenamines such as 14.

The preparation of the key intermediate 19 which on base treatment would be expected to yield 12 is shown in **Scheme 4**. In a typical experiment, the phenylethylamine 15a was condensed with 3-acetylpyridine and the intermediate imine 16a reduced by $NaBH_4$ to give the amine 17a which was acetylated to the amide 18a. The salt 19a isolated as bisperchlorate



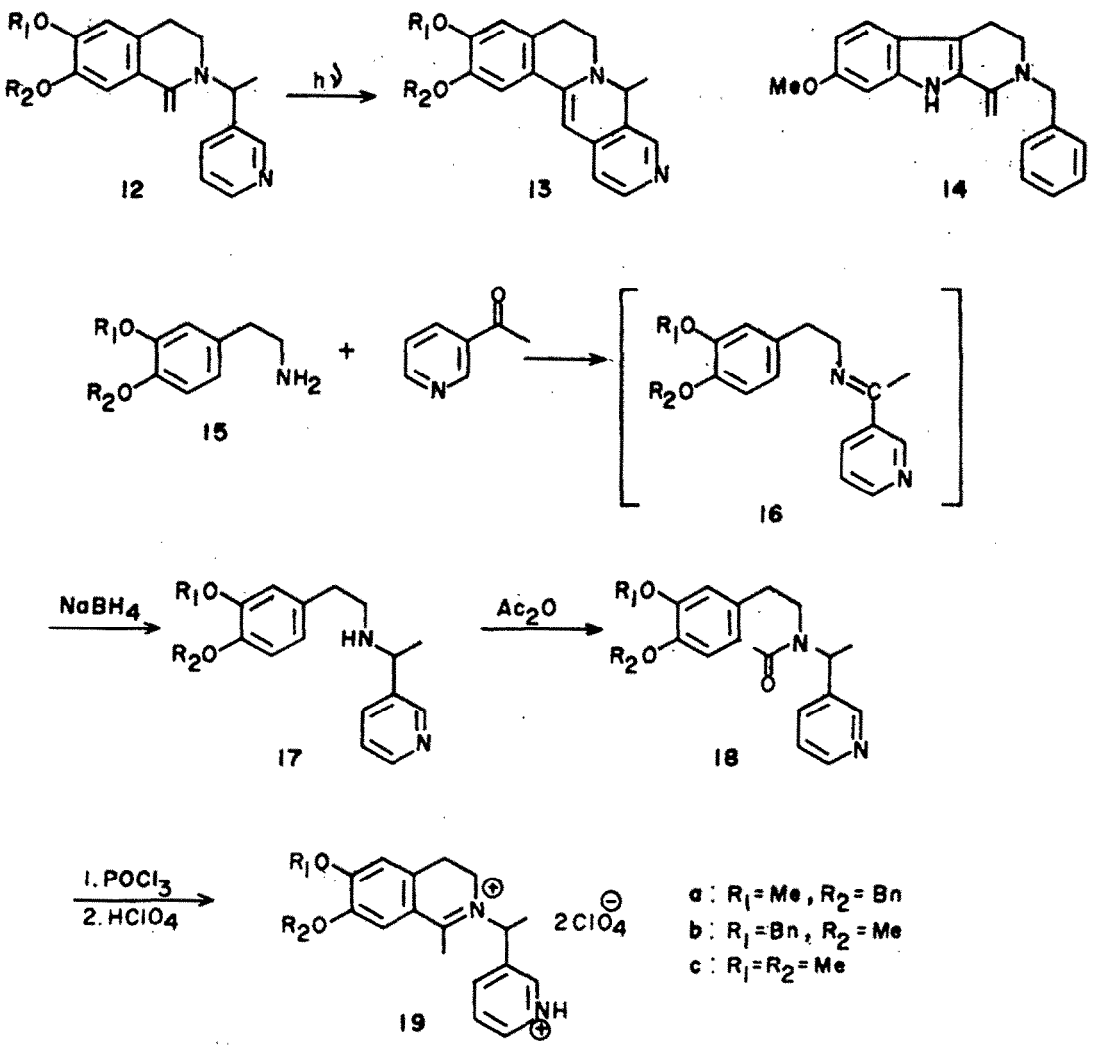
Scheme 3

was prepared in good yield by heating 18a with $POCl_3$ at 60-70°C. Unfortunately, the model enamine 12c generated from 19c by treatment with Et_3N could not be induced to undergo photocyclisation.

It was then envisaged that activation of the C-4 of the pyridine moiety in 12 by acylation could facilitate nucleophilic attack of the enamine double bond at this position resulting in the N-acyldihydropyridine intermediate 20 which could thereafter be converted to O-benzyldehydroalamaridine (21) by oxidation (**Scheme 5**).

In the model experiment, a suspension of 19c in $CHCl_3$ was stirred with Et_3N and the resulting solution treated with benzoyl chloride. Usual work-up and column chromatography of the reaction mixture, furnished a yellow compound in 6% yield, the spectral data of which were compatible with the expected compound 21c. However, the major component (25%) isolated was found to be 21d. Evidently, the desired cyclisation occurred but with concomitant benzoylation at C-13.

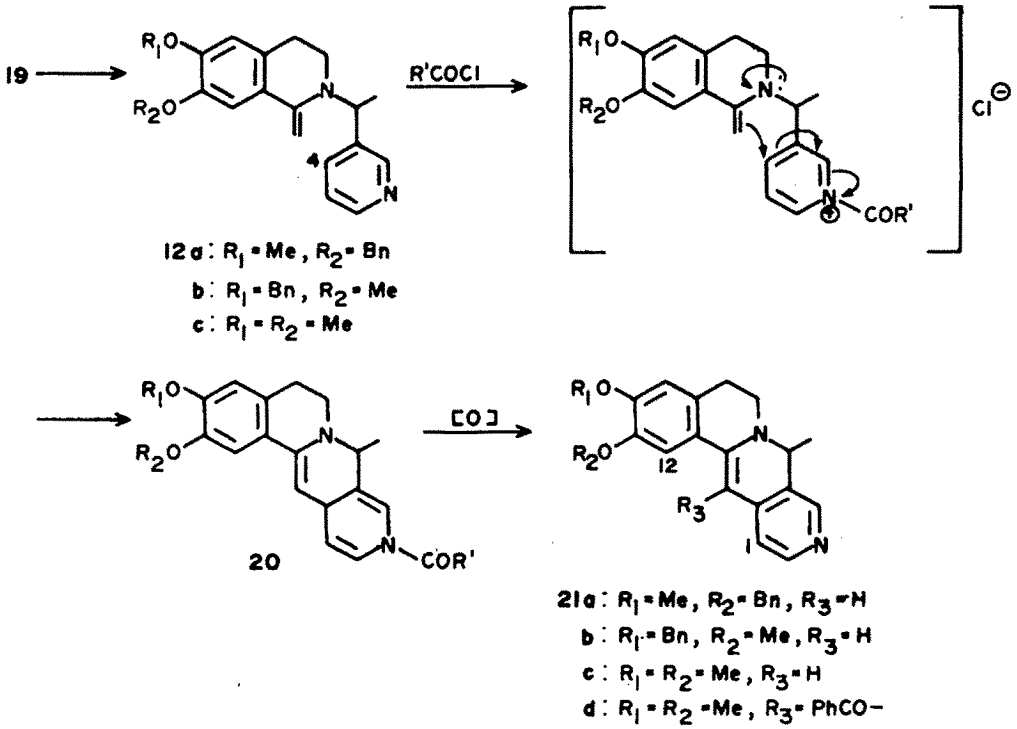
The unwanted acylation at C-13 could, however, be avoided by effecting the cyclisation using pivaloyl chlorode, a bulky enough acylating agent to be hindered by the hydrogens at C-1 and C-12. Thus, a suspension of 19c in $CHCl_3$ with Et_3N and pivaloyl chloride gave O-methyldehydroalamaridine (21c) as the only product in 12% yield. Similarly, 19a afforded 21a in 25% yield. The mass spectra of 21a and 21c exhibited strong M-15 peaks and the ^1H NMR spectra showed the olefinic 13-H's as singlets at around δ 5.70.



Scheme 4

Initial attempts to reduce the double bond in **21a** were rather frustrating. For example, reduction with $NaBH_4$ in methanol was very sluggish as indicated by TLC; hydrogenation in presence of either Pd/C or PtO_2 also proved futile. However, a smooth reduction could be achieved by sodium cyanoborohydride in acetic acid affording a mixture of two products **22a** and **23a** in 1:3 ratio. The assignment of their structures was based on comparison of the ^1H NMR spectral data with those of known 8-methyltetrahydroprotoberberines **24** and **25**, which were reported to have the chemical shift of the C-8 methyl at δ 1.40 and 1.54 respectively[11]. The minor compound obtained by the reduction of **21a** exhibited the methyl doublet at δ 1.42 and the major one at δ 1.58. They were accordingly assigned the structures **22a** and **23a** respectively. Interestingly, the reduction of **21a** by $NaBH_4$ in acetic acid gave almost exclusively **23a**. Apparently, triacetoxyborohydride, the reducing species by virture of its larger bulk, attacked the enamine moiety almost exclusively from the side opposite to that of C-5 methyl.

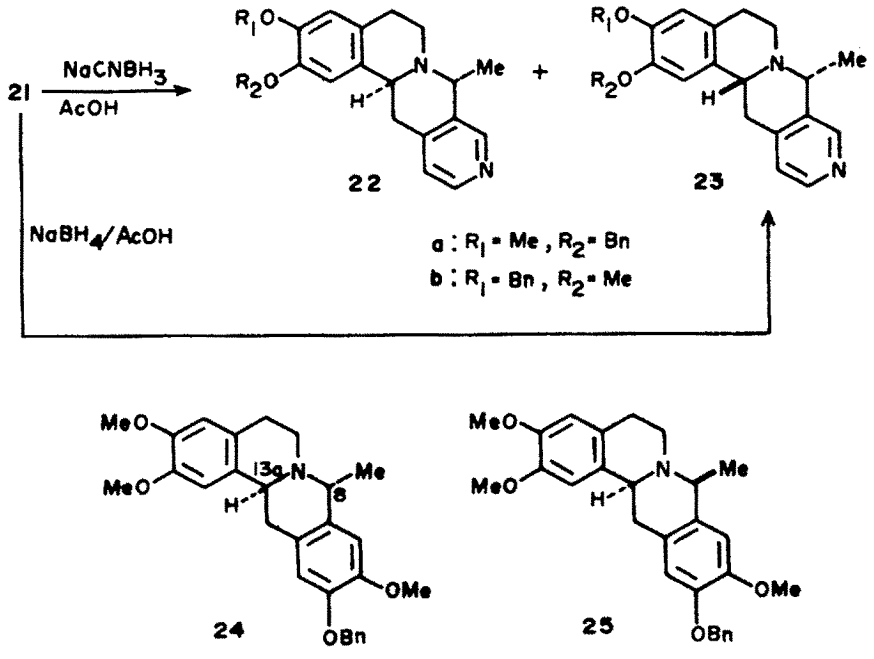
Finally, debenzylation of **22a** with ethanolic hydrochloric acid afforded a product, the spectral data (UV, IR, mass and ^1H NMR) of which were identical with those of alamaridine (**1**). Similarly, **23a** was debenzylated to 5-epi-alamaridine (**26**). Recently MacLean et al. reported the total synthesis of **1** following a different strategy[12].



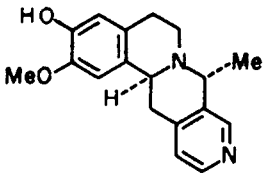
Scheme 5

Isoalamaridine (27) and iso-5-epi-alamaridine (28), the regioisomers of 1, were also identically synthesised. Although most of the features of the ^1H NMR spectrum of isoalamaridine were very similar to those of 1, they showed distinctly different chemical shifts for C-9 and C-12 hydrogen singlets.

Now,on the basis of NMR studies[11] and crystallographic evidences[13] Brossi et al. confirmed the dependence of the conformations of 8-methyltetrahydroprotoberberines on the configuration of the 8-methyl group. Thus, with cis related 13a-H and 8-CH_3, compound 24 assumes a cis quinolizine conformation while a trans one is preferred for the trans isomer 25. Accordingly,



alamaridine and isoalamaridine should have the conformation 29 while their 5-epimers could be assigned conformation 30.



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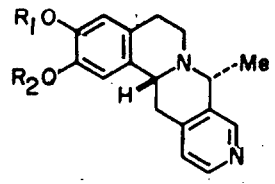
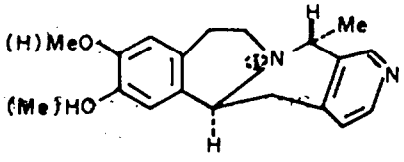


26: R_1 = Me, R_2 = H
28: R_1 = H , R_2 = Me



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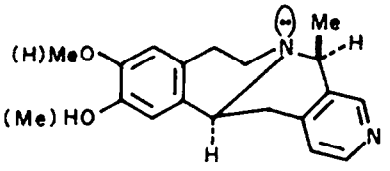

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EXPERIMENTAL

Melting points were determined in open capillaries in sulphuric acid bath and are uncorrected. IR spectra were recorded on a Perkin Elmer Model 177 spectrometer. UV spectra were registered on either Carl Zeiss Specord UV-VIS or Pye Unicam SP8-300 UV-VIS spectrophotometer. ^{1}H NMR spectra were measured with TMS as internal standard on Jeol FX-100 instrument and mass spectra on a Hitachi RMU-6L instrument.

Isolation of alamaridine (1) : Alamaridine was isolated from the weakly basic fraction of the A. lamarckii seed alkaloids. The details of the extraction procedure for A. lamarckii and isolation of other benzopyridoquinolizine alkaloids have already been described[3]. Briefly, the methanolic extract of the seeds (5 kg) of A. lamarckii was treated with 3N acetic acid and the acid extract was fractionated by successive extraction with buffers of pH 5.6 and 4.6 and finally with 2N HCl. The 2N HCl fraction was basified with aqueous NH_3 and extracted with $CHCl_3$. Concentration of the organic phase gave a gummy residue (6.5 g). The latter (4.0 g) was chromatographed over a column of deactivated silica gel.

Elution with petroleum ether (60°-80°C)-$CHCl_3$,$CHCl_3$ and CH_3OH-$CHCl_3$ (1:99) gave a residue which was combined with the mother liquors of crystallisation of other benzopyridoquinolizine alkaloids obtained from the fractions eluted with petroleum ether-$CHCl_3$ (50:50-25:75) and CH_3OH-$CHCl_3$ (1:99-2:98). This material (1.8 g) was chromatographed over silica gel and fraction eluted with $CHCl_3$ was crystallised from CH_3OH yielding alamaridine (1), light yellow needles (yield, 0.005 g, 0.0001%), m.p. 196°C, IR (KBr): νmax: 2920, 1590, 1500, 1360, 1330, 1260, 1130, 1020, 850, 830, 790, 730, 720 and 670 cm^{-1}; UV: λmax (EtOH) (log ϵ): 226 sh (3.85), 258 (3.35) and 286 (3.31) nm; (0.1 N NaOH); 245 sh (3.65) and 300 (3.28) nm; m/z (rel. int. %); 296 (M^+, 47), 295 (31), 282 (20), 281 (100), 279 (12), 177 (15), 176 (25), 163 (5), 162 (9), 120 (14), 119 (9) and 118 (8); ^{1}H NMR ($CDCl_3$) : δ 1.42 (d, J=6 Hz, 3H), 2.60 (m, 5H), 3.90 (s, 3H), 4.08-4.20 (m, 2H), 6.66 (s, 1H), 6.84 (s, 1H), 7.08 (d, J=6 Hz, 1H) 8.40 (d, J=6 Hz , 1H) and 8.44 (s, 1H).

Oxidation of alamaridine (1) with iodine: A solution of (1) (0.001g) in ethanol (1 ml) was refluxed with iodine (0.002 g) for 3 h. Excess iodine was removed by treatment with aqueous sodium thiosulfate solution. The reaction mixture was purified by preparative TLC : λmax (EtOH) : 228, 260, 285 sh and 368 nm; (0.1 N NaOH) : 231, 259, 366 and 408 nm; (0.1 N HCl) : 225, 270, 305 sh and 425 nm.

7-Benzyloxy-6-methoxy-1-methylene-2-nicotinyl-1,2,3,4-tetrahydroisoquinoline (7): To a slurry of sodium nicotinate (9.0 g, 0.06 mol) in dry benzene (50 ml), oxalyl chloride (6ml, 0.07 mol) was added dropwise and the reaction mixture was refluxed for 1 h. After distilling off the solvent under reduced pressure, nicotinyl chloride was obtained as a viscous liquid. A solution of the latter in benzene (100 ml) was added to a stirred solution of 7-benzyloxy-6-methoxy-1-methyl-3,4-dihydroisoquinoline[14] (11.0 g, 0.04 mol) in benzene (200 ml) containing Et_3N (80 ml). The reaction mixture was kept overnight at room temperature and then in ice water for 1 h. The precipitated triethylamine hydrochloride was filtered and the filtrate distilled under reduced pressure. The solid obtained was crystallised from $CHCl_3$-petroleum ether to furnish the enamide 7 (11.5 g, 76%) as light yellow needles, m.p. 142-144°C; νmax (Nujol): 1635, 1605 and 1595 cm^{-1}; λmax (EtOH): 235 (4.00), 264 (4.17) and 300 (3.87) nm; m/z: 386(M^+, 7), 358 (24), 295 (19), 267 (96) and 91 (100); ^{1}H NMR ($CDCl_3$): δ 2.98 (t, J=6 Hz, 2H), 3.88 (s, 3H), 4.12 (t, J=6 Hz, 2H), 4.32 (d, J=1.5 hZ, 1H), 5.12 (s, 2H), 5.14 (d, J=1.5 Hz, 1H), 6.66 (s, 1H), 7.02 (s, 1H), 7.16-7.56 (m, 6H), 7.64-7.84 (m, 1H) and 8.56-8.64 (m, 2H). (Calc. for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.31; H, 5.52; N, 7.49.)

11-Benzyloxy-10-methoxy-7,8-dihydro-5H-benzo[a]pyrido[3,4-g]quinolizin-5-one (8) and 11-benzyloxy-10-methoxy-7,8-dihydro-5H-benzo[a]pyrido[3,2-g]quinolizin-5-one (9): A solution of the enamide 7 (2.0 g, 0.005 mol) in benzene (340 ml) was irradiated under nitrogen for 4.5 h at 15-20°C in an immersion-well type photoreactor with a 16 W low pressure mercury lamp. After the irradiation was over, benzene was removed under reduced pressure. An additional 9.4 g of 7 was similarly irradiated in five batches. The products from all the batches were combined and chromatographed over deactivated silica gel. Elution with $CHCl_3$ afforded a brown solid (4.8 g) which showed two close spots on TLC. The mixture was rechromatographed over silica gel. Elution with $CHCl_3$-petroleum ether (25:75-50:50) gave the faster moving lactam as a light brown solid which on crystallisation from $CHCl_3$-petroleum ether yielded 9(0.75 g, 7%) as yellow needles, m.p. 162-164°C; ν max (Nujol): 1650, 1600, 1565 and 1512 cm^{-1}; λ max (EtOH): 240 (4.07), 256 sh (3.93), 275 sh (3.77) and 342 (4.38) nm; m/z: 384 (M^+,10), 293 (14), 243 (10), 223 (10), 205 (10), 106 (56), 105 (50), 102 (36), 101 (35), 92 (41) and 91 (100); ^{1}H NMR ($CDCl_3$): δ 2.96 (t, J=6 Hz, 2H), 3.92 (s, 3H), 4.34 (t, J=6 Hz, 2H), 5.20 (s, 2H), 6.76 (s, 1H), 7.04 (s, 1H), 7.12-7.58 (m, 7H), 8.64 (dd, J=8, 2Hz, 1H) and 8.87 (dd, J=6, 2 Hz, 1H). (Calc. for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 75.13; H, 5.07; N, 7.53.)

Elution with $CHCl_3$-petroleum ether (50:50-75:25) furnished the slower moving lactam as a light brown solid crystallising from $CHCl_3$-petroleum ether to give light brown granules of 8 (3.1 g, 27%), m.p. 180-182°C; ν max (Nujol): 1665, 1650, 1605 and 1510 cm^{-1}; λmax(EtOH): 245 (4.16), 280 sh (3.77), 355 (4.44) and 370 sh (4.37) nm; m/z: 384 (M^+, 48), 293 (42), 265 (33), 250 (14), 249 (13), 221 (35), 191 (17), 179 (17), 169 (17), 135 (24), 106 (55), 92 (50) and 91 (100); ^{1}H NMR ($CDCl_3$): δ 2.92 (t, J=6 Hz, 2H), 3.90 (s, 3H), 4.30 (t, J=6 Hz, 2H), 5.17 (s, 2H), 6.52 (s, 1H), 6.72 (s, 1H), 7.12-7.52 (m, 7H), 8.58 (d, J=6 Hz, 1H) and 9.48 (s, 1H). (Calc. for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.69; H, 5.49; N, 7.41.)

11-Benzyloxy-10-methoxy-7,8-dihydro-5H-benzo[a]pyrido[3,4-g]quinolizin-5-thione (10): To a stirred solution of the lactam 8 (3.0 g, 0.008 mol) in pyridine (75 ml) phosphorus pentasulfide (5.5 g) was added and the mixture refluxed for 12 h. The reaction mixture was poured on to ice with stirring and then extracted with $CHCl_3$ (3x100 ml), washed with water (2x150 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the

material obtained was chromatographed over deactivated silica gel. Elution with $CHCl_3$ and CH_3OH-$CHCl_3$ (1:99) yielded thiolactam **10** (2.0 g, 64%) as a yellow solid which crystallised from $CHCl_3$-CH_3OH as yellow needles, m.p. 186-188°C; νmax (Nujol): 1602, 1585 and 1512 cm^{-1}; λmax (EtOH): 248 (4.28), 266 (4.18), 281 sh (4.17), 292 sh (4.10), 328 (4.16) and 380 (4.26) nm; m/z: 400 (M^+,5), 310 (11), 309 (48), 249 (15), 237 (37), 205 (29), 92 (47) and 91 (100); ^{1}H NMR ($CDCl_3$): δ 3.00 (t, J=6 Hz, 2H), 2.92 (s, 3H), 5.00 (t, J=6 Hz, 2H), 5.20 (s, 2H), 6.76 (s, 1H), 6.84 (s, 1H), 7.28-7.52 (m, 7H), 8.58 (d, J=6 Hz, 1H) and 10.08 (s, 1H). (Calc. for $C_{24}H_{20}N_2O_2S$: C, 71.99; H, 5.03; N, 7.00. Found: C, 71.75; H, 5.19; N, 7.17.)

N-[1-(3'-Pyridyl)]ethyl-2-(4-benzyloxy-3-methoxy)phenylethylamine (17a): A solution of 2-(4-benzyloxy-3-methoxy)phenylethylamine **15a** (14.0 g, 0.054 mol) and 3-acetylpyridine (7.3 g, 0.06 mol) in dry benzene (70 ml) was refluxed for 9 h using a Dean-Stark apparatus for removal of water. Solvent was removed under reduced pressure and the residual oil was dried under vacuum. To a solution of the residue in methanol (150 ml) was added $NaBH_4$ (3.0 g) in portions at 0°C. After the addition was over, the solution was kept at room temperature for 2 h. The reaction mixture was diluted with water (100 ml) and extracted with chloroform (3x100 ml). The organic phase was washed with water and brine, and evaporated to give an oil (20.0 g). The latter was chromatographed over neutral alumina. Elution with petroleum ether, $CHCl_3$ and $CHCl_3$-CH_3OH(90:10) gave **17a** (17.0 g, 86%) as a viscous oil; νmax (neat): 3300, 1605, 1590 and 1515 cm^{-1}; m/z: 362 (M^+, 14), 228 (100), 165 (55), 135 (95), 106 (95) and 91 (91); ^{1}H NMR ($CDCl_3$): δ 1.28 (d, J=6 Hz, 3H), 2.70 (bs, 4H), 3.80 (q, J=6 Hz, 1H), 3.84 (s, 3H), 5.12 (s, 2H), 6.56-6.88 (m, 3H), 7.16-7.36 (m, 6H), 7.60 (m, 1H) and 8.44-8.60 (m, 2H).

N-[1-(3'-Pyridyl)]ethyl-2-(3,4-dimethoxy)phenylethylamine (17c): The amine **17c** was prepared by the same method as for **17a** i.e. by refluxing 2-(3,4-dimethoxy)phenylethylamine **15c** (5.4 g, 0.02 mol), 3-acetylpyridine (3.8 g, 0.031 mol) in benzene (50 ml), reducing the product in ethanol (40 ml) with $NaBH_4$ (2.0 g). After usual work up, the crude amine **17c** (10.0 g) was obtained as a viscous oil which was acetylated as described later without further purification; νmax (neat): 3300, 1605, 1590 and 1515 cm^{-1}; m/z: 286 (M^+, 6), 165 (18), 152 (94) 151 (70), 135 (100) and 106 (100); ^{1}H NMR ($CDCl_3$): δ 1.32 (d, J=6 Hz, 3H), 2.72 (bs, 4H), 3.80 (q, J=6 Hz, 1H), 3.84 (s, 6H), 6.64-6.84 (m, 3H), 7.16-7.36 (m, 1H), 7.52-7.68 (m, 1H) and 8.40-8.60 (m, 2H).

N-Acetyl-N-[1-(3'-pyridyl)]ethyl-2-(4-benzyloxy-3-methoxy)phenylethylamine (18a): A solution of the amine **17a** (17.0 g, 0.05 mol) in pyridine (75 ml) was treated with acetic anhydride (40 ml) at 0°C and then kept at room temperature for 48 h. The reaction mixture was treated with water (5 ml) and poured into ice-water (400 ml). Extraction with $CHCl_3$ (3x300 ml), repeated washing of the organic phase with water, drying over anhydrous Na_2SO_4 and finally evaporation of the solvent left an oil from which excess pyridine was removed by distillation under reduced pressure. The residual oil was chromatographed over neutral alumina. Elution with petroleum ether-$CHCl_3$ (50:50), $CHCl_3$ and $CHCl_3$-CH_3OH (98:2) gave an oil which solidified on trituration with petroleum ether to furnish **18a** (13.8 g, 73%). Crystallisation from $CHCl_3$-petroleum ether yielded white granules of **18a**, m.p. 128-130°C; νmax (Nujol): 1630, 1600, 1585, 1570 and 1510 cm^{-1}; m/z: 404 (M^+, 3), 240 (85), 177 (8), 165 (19), 135 (80), 106 (95) and 91 (100); ^{1}H NMR ($CDCl_3$): δ 1.60 (d, J=6 Hz, 3H), 2.16 and 2.28 (pair of singlets, 3H), 2.32-2.92 (m, 2H), 3.00-3.24 (m, 2H), 3.84 (s, 3H), 5.08 (s, 2H), 5.08 and 6.00 (pair of quartets, J=6 Hz, 1H), 6.36-6.88 (m, 3H), 7.20-7.80 (m, 7H) and 8.48-8.72 (m, 2H). The pair of singlets at δ 2.16 and 2.28 for -N-COCH_3 and that of quartets at δ 5.08 and 6.00 for N-CH-CH_3 are due to restricted rotation around the amide bond. This was verified by taking the spectrum at 55°C in DMSO-d_6 when both the singlets and the quartets coalesced. (Calc. for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.47; H, 6.89; N, 6.83.)

N-Acetyl-N-[1-(3'-pyridyl)]ethyl-2-(3-benzyloxy-4-methoxy)phenylethylamine (18b) : N-[1-3'-Pyridyl)]ethyl-2-(3-benzyloxy-4-methoxy)phenylethylamine (17b) was made similarly as amine **17a** i.e. by refluxing 2-(3-benzyloxy-4-methoxy)phenylethylamine (15b) (16.0 g, 0.062 mol)

and 3-acetylpyridine (8.4 g, 0.069 mol) in benzene (80 ml) and reducing the intermediate imine with $NaBH_4$ (4.5 g) in CH_3OH (200 ml). The amine **17b** (23 g) obtained as an oil was converted without purification to its N-acetyl derivative (**18b**) following the same procedure as for the preparation of the amide **18a**. Thus a part (16.0 g) of the crude amine **17b** was treated with acetic anhydride (40 ml) in pyridine (75 ml). After usual work-up the amide **18b** (14.3 g, 80%) was obtained as a viscous oil; νmax (neat): 1640, 1595, 1585 and 1515 cm^{-1}; m/z: 404 (M^+, 9), 240 (100), 177 (8), 165 (56), 164 (57), 135 (62), 106 (82) and 91 (82); ^1H NMR ($CDCl_3$): δ 1.56 (d, J=6 Hz, 3H), 2.12 and 2.24 (pair of singlets, 3H), 2.32-2.80 (m, 2H), 3.00-3.32 (m, 2H), 3.84 (s, 3H), 5.08 (s, 2H), 5.08 and 6.00 (pair of quartets, J=6 Hz, 1H), 6.40-6.84 (m, 3H), 7.20-7.68 (m, 7H) and 8.24-8.68 (m, 2H).

N-Acetyl-N-[1-(3'-pyridyl)]ethyl-2-(3,4-dimethoxy)phenylethylamine (18c): The amide **18c** was made by the same procedure as for **18a** using the crude amine **17c** (10.0 g), acetic anhydride (10 ml) and pyridine (50 ml). Chromatography of the product on silica gel and elution with $CHCl_3$ and $CHCl_3$-CH_3OH (99:1) gave **18c** (6.5 g, 57%) as a viscous oil; νmax (neat): 1630, 1590 and 1510 cm^{-1}; m/z: 328 (M^+, 20), 177 (14), 165 (80), 164 (100), 151 (68), 135 (68) and 106 (74); ^1H NMR ($CDCl_3$): δ 1.60 (d, J-6 Hz, 3H), 2.16 and 2.24 (pair of singlets, 3H), 2.40-2.96 (m, 2H), 3.00-3.60 (m, 2H) 3.84 (s, 6H), 5.12 and 6.00 (pair of quartets, J=6 Hz, 1H), 6.20-6.88 (m, 3H), 7.20-7.40 (m, 1H), 7.48-7.80 (m, 1H) and 8.48-8.72 (m, 2H).

7-Benzyloxy-6-methoxy-1-methyl-2-[1-(3'-pyridyl)]ethyl-3,4-dihydroisoquinolinium bisperchlorate (19a): A suspension of the amide **18a** (1.0 g, 0.002 mol) in $POCl_3$ (5 ml) was heated at 60-70°C with stirring. During heating, the amide **18a** dissolved, but another solid appeared after 15 to 20 min, and heating continued for 3 h. Excess $POCl_3$ was removed by distillation under reduced pressure. The residual solid after drying under vacuum was taken in EtOH (10 ml) and cooled in ice-water. To this solution was added a solution of 60% $HClO_4$ (0.5 ml) and cooled. The precipitated salt was filtered and washed with alcohol and ether and dried under vacuum. The material was boiled with EtOH-MeOH (50:50) (5 ml), filtered and dried under vacuum to afford the salt **19a** (1.1 g, 63%) as a pale yellow solid an aliquot of which was crystallised from EtOH to give pale yellow granules, m.p. 225-226°C; νmax (KBr): 2600, 1605, 1550 and 1510 cm^{-1}; λmax (EtOH): 257 (3.88), 310 (4.07) and 360 (4.08) nm; ^1H NMR (DMSO-d_6): δ 1.92 (d, J=6 Hz, 3H), 3.04 (s, 3H), 2.76-4.00 (m, 4H), 3.92 (s, 3H), 5.24 (s, 2H), 6.20 (q, J=6 Hz, 1H), 7.16 (s, 1H), 7.28-7.64 (m, 5H), 7.72 (s, 1H), 7.92 (dd, J=8, 6 Hz, 1H), 8.52 (d, J=8 Hz, 1H), 8.88 (d, J=6 Hz, 1H) and 9.04 (s, 1H). (Calc. for $C_{25}H_{28}Cl_2N_2O_{10}$: C, 51.12; H, 4.80; N, 4.76. Found: C, 51.27; H, 4.65; N, 4.58.)

6-Benzyloxy-7-methoxy-1-methyl-2-[1-(3'-pyridyl)]ethyl-3,4-dihydroisoquinolinium bisperchlorate (19b): The title compound was prepared by the same procedure as for **19a** from the amide **18b** (10.0 g, 0.02 mol) and $POCl_3$ (15 ml) and obtained as a yellow solid (6.0 g, 51 %), m.p. 228-230°C; νmax (KBr): 2500, 1605, 1550 and 1520 cm^{-1}; λmax (EtOH): 260 (3.76), 310 (3.93) and 365 (3.88) nm; ^1H NMR (DMSO-d_6): δ 1.88 (d, J=6 Hz, 3H), 2.76-4.00 (m, 4H), 3.08 (s, 3H), 3.92 (s, 3H), 5.28 (s, 2H), 6.20 (q, J=6 Hz, 1H), 7.24 (s, 1H), 7.28-7.60 (m, 5H), 7.60 (s, 1H), 7.84 (dd, J=8, 6 Hz, 1H), 8.44 (d, J=8 Hz, 1H), 8.84 (d, J=6 Hz, 1H) and 9.00 (s, 1H). (Calc. for $C_{25}H_{28}Cl_2N_2O_{10}$: C, 51.12; H, 4.80; N, 4.76. Found: C, 51.05; H, 4.92; N, 4.91.)

6,7-Dimethoxy-1-methyl-2-[1-(3'-pyridyl)]ethyl-3,4-dihydroisoquinolinium bisperchlorate (19c): The salt **19c** was prepared by the same procedure as for **19a** from the amide **18c** (6.5 g, 0.02 mol) and $POCl_3$ (15 ml) and obtained as a yellow solid (5.0 g, 49%), crystallising from EtOH-MeOH as yellow granules, m.p. 228-230°C; νmax (KBr): 2550, 1605, 1550 and 1520 cm^{-1}; λmax (EtOH): 252 (3.91), 307 (4.02) and 360 (4.03) nm; ^1H NMR (DMSO-d_6): δ 1.92 (d, J=6 Hz, 3H), 2.76-4.08 (m, 4H), 3.08 (s, 3H), 3.88 (s, 6H), 6.24 (q, J=6 Hz, 1H), 7.16 (s, 1H), 7.60 (s, 1H), 8.00 (dd, J=8, 6 Hz, 1H), 8.64 (d, J=8 Hz, 1H), 8.92 (d, J=6 Hz, 1H) and 9.12 (s, 1H). (Calc for $C_{19}H_{24}Cl_2N_2O_{10}$: C, 44.63; H, 4.73; N, 5.48. Found: C, 44.42; H, 4.53; N, 5.82.)

Cyclisation of 19c in presence of benzoyl chloride: To a suspension of the salt **19c** (0.30 g, 0.0006 mol) in $CHCl_3$ (20 ml) under nitrogen and at 0°C was added Et_3N (1 ml). The resulting greenish yellow solution was treated with a solution of benzoyl chloride (0.2 ml) in $CHCl_3$ (10 ml) at 0°C and stirred for 3 h. The deep red reaction mixture was washed with water, brine and dried over Na_2SO_4. Removal of solvent afforded a deep yellow residue which on chromatography over basic alumina and elution with petroleum ether-$CHCl_3$ (25:75) gave O-methyldehydroalamaridine (**21c**) as a gummy residue (0.01 g, 6%) showing a single spot on TLC with a bright green fluorescence in UV light; ν max (KBr):1600, 1580 and 1500 cm^{-1}; λ max (EtOH): 235 sh (4.03), 260 (3.68), 275 (3.59), 285 (3.52), 306 (3.02) and 403 (3.76) nm; m/z: 308 (M^+, 70), 294 (50), 293 (100) and 277 (60); ^1H NMR ($CDCl_3$): δ 1.28 (d, J=6 Hz, 3H), 2.76-3.00 (m, 2H), 3.16-3.68 (m, 2H), 3.88 (s, 3H), 3.92 (s, 3H), 4.64 (q, J=6 Hz, 1H), 5.76 (s, 1H), 6.68 (s, 1H), 6.80 (d, J=6 Hz, 1H), 7.20 (s, 1H), 8.12 (s, 1H) and 8.24 (d, J=6 Hz, 1H).

Further elution with $CHCl_3$ and $CHCl_3$-CH_3OH (99:1) yielded O-methyl-13-benzoyldehydroalamaridine (**21d**) (0.06 g, 25%) as a yellow solid, m.p. 133-135°C; ν max (KBr): 1605, 1580, 1560, 1510 and 1500 cm^{-1}; λ max (EtOH): 234 (4.10), 255 sh (3.91), 280 sh (3.66), 332 (3.93) and 410 (3.70)nm; m/z: 412 (M^+, 25) and 397 (100); ^1H NMR ($CDCl_3$): δ 1.60 (d, J=6 Hz, 3H), 2.56-3.24 (m, 2H) 3.48-3.80 (m, 2H), 3.64 (s, 3H), 3.76 (s, 3H), 4.80 (q, J=6 Hz, 1H), 6.48 (s, 1H), 6.88 (s, 1H), 6.96-7.24 (m, 3H), 7.52-7.68 (m, 2H), 8.08 (d, J=6 Hz, 1H), 8.20 (s, 1H) and 8.36 (d, J=6 Hz, 1H). (Calc. for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79. Found : C, 75.53; H, 5.67; N, 6.91.)

Cyclisation of 19c in presence of pivaloyl chloride: A suspension of the salt **19c** (0.5 g, 0.001 mol) in CH_2Cl_2 (20 ml) was treated with Et_3N (1 ml) at 0°C. To the green solution produced, a solution of pivaloyl chloride (0.15 ml) in CH_2Cl_2 (5 ml) was added at 0°C with stirring and the reaction mixture was kept at 30°C for 1 h. The deep red mixture was concentrated and chromatographed over basic alumina. Elution with $CHCl_3$ afforded **21c** as a deep yellow gummy residue (0.04 g, 12%).

O-Benzyldehydroalamaridine (21a): A suspension of the salt **19a** (3.0 g, 0.005 mol) in $CHCl_3$ (75 ml) was treated with Et_3N (9 ml) at 0°C. To the resulting solution was added at 0°C pivaloyl chloride (0.75 ml) in $CHCl_3$ (15 ml) dropwise with stirring. After the addition was over the reaction mixture was kept at 30°C for 2 h. The reaction mixture was washed with water (3x100 ml) and brine (1x150 ml). After drying over Na_2SO_4 solvent was removed under reduced pressure. The deep red gummy residue was chromatographed over basic alumina. Elution with petroleum ether-$CHCl_3$ (25:75) and $CHCl_3$ afforded O-benzyldehydroalamaridine (**21a**) (0.48 g, 25%) as a yellow gummy residue. A part of the material was crystallised from petroleum ether to give pale yellow granules of **21a**, m.p. 114-116°C; ν max (KBr): 1600, 1580 and 1500 cm^{-1}; λ max (EtOH): 240 (3.77), 258 (3.82), 275 sh (3.85), 285 (3.87), 308 (3.63), 322 sh (3.53) and 402 (4.12) nm; m/z: 384 (M^+, 20), 382 (20), 370 (22), 369 (86) and 91 (100); ^1H NMR ($CDCl_3$): δ 1.24 (d, J=6 Hz, 3H), 2.68-3.04 (m, 2H), 3.04-3.68 (m, 2H), 3.88 (s, 3H), 4.60 (q, J=6 Hz, 1H), 5.20 (s, 2H), 5.60 (s, 1H), 6.68 (s, 1H), 6.76 (d, J=6 Hz, 1H), 7.24 (s, 1H), 7.24-7.64 (m, 5H), 8.08 (s, 1H) and 8.24 (d, J=6 Hz, 1H). (Calc. for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29. Found : C, 78.25; H, 6.34; N, 7.08.)

O-Benzyldehydroisoalamaridine (21b) : The title compound was prepared by the same procedure as for **21a** from the salt **19b** (5.0 g, 0.009 mol), pivaloyl chloride (1.25 ml) and Et_3N (15 ml) in $CHCl_3$ (110 ml). After chromatography of the reaction mixture on basic alumina, O-benzyldehydroisoalamaridine (**21b**) (0.60 g, 18%) was obtained as a yellow gummy material; ν max (KBr): 1600, 1580 and 1510 cm^{-1}; λ max (EtOH): 275 (4.29), 307 (4.21) and 402 (4.10) nm; m/z: 384 (M^+, 4), 382 (2), 370 (6), 369 (22) and 91 (100); ^1H NMR ($CDCl_3$): δ 1.24 (d, J=6 Hz, 3H), 2.70-3.70 (m, 4H), 3.92 (s, 3H), 4.60 (q, J=6 Hz, 1H), 5.16 (s, 2H), 5.72 (s, 1H), 6.64 (s, 1H), 6.80 (d, J=6 Hz, 1H), 7.20 (s, 1H), 7.20-7.60 (m, 5H), 8.08 (s, 1H) and 8.20 (d, J=6 Hz, 1H).

O-Benzylalamaridine (22a) and O-benzyl-5-epi-alamaridine (23a) : To a solution of **21a** (0.20 g, 0.005 mol) in glacial acetic acid (10 ml) at 5-10°C was added in portions sodium cyanoborohydride (0.15 g). The reaction was monitored by TLC and when the latter showed complete disappearance of **21a** (2 h), water (20 ml) was added to the reaction mixture and neutralised with solid Na_2CO_3. Extraction with $CHCl_3$ (3x50 ml), washing the organic phase with water (2x50 ml) and brine (100 ml), and finally drying over Na_2SO_4 afforded a gummy residue (0.20 g) TLC of which showed it to be a mixture of **22a** and **23a**. Purification by preparative TLC on silica gel in diethylamine-ethylacetate (0.5:99.5) gave O-benzyl-5-epi-alamaridine (**23a**) (0.10 g,50%), the faster moving compound as a gummy material; νmax (KBr): 1600 and 1510 cm^{-1}; m/z: 386 (M^+, 60), 385 (39), 371 (100), 369 (66), 295 (35), 291 (33), 280 (35), 279 (30), 278 (33), 265 (19), 119 (11), 118 (13) and 91 (88); ^1H NMR ($CDCl_3$): δ 1.56 (d, J=6 Hz, 3H), 2.20-3.48 (m, 6H), 3.60-3.96 (m, 2H), 3.84 (s, 3H), 5.12 (s, 2H), 6.64 (s, 1H), 6.72 (s, 1H), 7.00 (d, J=6 Hz, 1H), 7.28-7.60 (m, 5H), 8.36 (d, J=6 Hz, 1H) and 8.48 (s, 1H).

The slower moving compound obtained as a gummy material was found to be O-benzylalamaridine (**22a**) (0.04 g, 20%); νmax (KBr): 1600 and 1510 cm^{-1}; m/z: 386 (M^+, 17), 385 (10), 371 (25), 295 (10), 279 (7), 265 (7), 120 (90), 119 (60), 118 (90) and 91 (100); ^1H NMR ($CDCl_3$): δ 1.40 (d, J=6 Hz, 3H), 2.72-3.20 (m, 4H), 3.88 (s, 3H), 4.08-4.40 (m, 2H), 5.16 (s, 2H), 6.48 (s, 1H), 6.52 (s, 1H), 7.04 (d, J=6 Hz, 1H), 7.28-7.60 (m, 5H), 8.36 (d, J=6 Hz, 1H) and 8.40 (s, 1H).

O-Benzylisoalamaridine (22b) and O-benzyliso-5-epi-alamaridine (23b): The reduction of O-benzyldehydroisoalamaridine (**21b**) (0.40 g, 0.001 mol) with sodium cyanoborohydride (0.18 g) in acetic acid (5.5 ml) was carried out in the same manner as for **21a** affording after preparative TLC of the crude reaction product, O-benzylisoalamaridine (**22b**) (0.04 g, 15%) as a gummy material which crystallised from petroleum ether, m.p. 88-90°C; νmax (KBr): 1605 and 1515 cm^{-1}; m/z: 386 (M^+, 7), 371 (8), 369 (9), 295 (19), 279 (23), 278 (12), 119 (13), 118 (8) and 91 (100); ^1H NMR ($CDCl_3$): δ 1.40 (d, J=6 Hz, 3H), 2.60-3.24 (m, 6H), 3.84 (s, 3H), 4.04-4.36 (m, 2H), 5.12 (s, 2H), 6.64 (s, 1H), 6.70 (s, 1H), 7.00 (d, J=6 Hz, 1H), 7.24-7.56 (m, 5H), 8.32 (d, J=6 Hz, 1H) and 8.36 (s, 1H), (Calc. for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.43; H, 6.59; N, 7.38)and O-benzyliso-5-epi-alamaridine (**23b**) (0.13 g, 33%) as a gummy material, crystalising from petroleum ether, m.p. 124-126°C; νmax (KBr): 1600 and 1510 cm^{-1}; m/z: 386 (M^+, 5), 371 (6), 369 (5), 295 (7), 279 (13), 278 (6), 119 (7), 118 (4) and 91 (100); ^1H NMR ($CDCl_3$): δ 1.60 (d, J=6 Hz, 3H), 2.32-3.48 (m, 6H), 3.60-3.96 (m, 2H), 3.88 (s, 3H), 5.12 (s, 2H), 6.64 (s, 1H), 6.72 (s, 1H), 7.04 (d, J=6 Hz, 1H), 7.24-7.52 (m, 5H), 8.32 (d, J=6 Hz, 1H) and 8.44 (s, 1H). (Calc. for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found C, 77.31; H, 6.89; N, 7.12.)

Alamaridine (1): A solution of O-benzylalamaridine (**22a**) (0.04 g, 0.0001 mol) in 50% ethanolic HCl (1.2 ml) was refluxed for 1 h. The reaction mixture was diluted with water and extracted with ether to remove the benzyl chloride formed. The aqueous part was then neutralised with $NaHCO_3$ and extracted with $CHCl_3$. After washing the organic phase with water and brine the solution was evaporated. The solid residue (0.01 g, 34%) obtained was crystallised from MeOH to give (±) alamaridine (**1**) as pale yellow granules, m.p.242-244°C; the spectral data for the synthetic material were identical with those for the natural product. (Calc. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9,45. Found : C, 72.77; H, 6.76; N, 9.35.)

5-Epi-alamaridine (26): The debenzylation of O-benzyl-5-epi-alamaridine (**23a**) (0.06 g, 0.00015 mol) was effected exactly as above using 50% ethanolic HCl (2 ml). 5-Epi-alamaridine (**26**) (0.015 g, 34%) obtained was crystallised from methanol as yellow granules, m.p. 220-222°C; νmax (KBr): 3120, 1615, 1595, 1570 and 1510 cm^{-1}; λmax EtOH): 225 sh (3.99), 258 (3.47), 266 (3.52), and 285 (3.68) nm; (0.1 N NaOH): 242 (4.06) and 300 (3.84) nm; m/z : 296 (M^+,28), 295 (28), 282 (16), 281 (100), 279 (28), 266 (6), 265 (3), 264 (6), 178 (8), 177(22), 176 (34), 121 (12), 120 (30), 119 (31) and 118 (31); ^1H NMR ($CDCl_3$): δ 1.60 (d, J=6 Hz, 3H), 2.32-3.56 (m, 6H), 3.60-4.00 (m, 2H), 3.92 (s, 3H), 6.64 (s, 1H), 6.84 (s, 1H), 7.08 (d, J=6 Hz, 1H), 8.36 (d, J=6 Hz, 1H) and 8.52 (s, 1H). (Calc. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80;

N, 9.45. Found C, 73.19; H, 6.59; N, 9.59.)

Isoalamaridine (27): O-benzylisoalamaridine (22b) (0.02 g, 0.00005 mol) was debenzylated in the same manner as 23a by refluxing with 50% ethanolic HCl (1 ml) to give a yellow solid which was crystallised from methanol to furnish yellow granules of isoalamaridine (27) (0.006 g, 41%), m.p. 196-198°C; νmax (KBr): 1600 and 1510 cm^{-1}; λmax (EtOH): 260 (3.40), 265 (3.39) and 282 (3.44) nm; (0.1 N NaOH): 260 (3.28) and 300 (3.43) nm; m/z: 296 (M^+, 60), 295 (46), 281 (100), 177 (24), 176 (36), 119 (14) and 106 (34); ^{1}H NMR ($CDCl_3$): δ 1.40 (d, J=6 Hz, 3H), 2.52-3.24 (m, 6H), 3.84 (s, 3H), 4.04-4.36 (m, 2H), 6.64 (s, 1H), 6.66 (s, 1H), 7.00 (d, J=6 Hz, 1H) and 8.20-8.36 (m, 2H). (Calc. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.71; H, 6.92; N, 9.32.)

Iso-5-epi-alamaridine (28): O-benzyliso-5-epi-alamaridine (23b) (0.05 g, 0.00013 mol) was debenzylated as above by refluxing with 50% ethanolic HCl (2 ml) to give after crystallisation from methanol iso-5-epi-alamaridine (28) (0.02 g, 52%), m.p. 202-204°C; νmax (KBr): 1600 and 1510 cm^{-1}; λmax (EtOH): 260 (2.88), 267 (2.87) and 285 (2.83) nm; (0.1 N NaOH): 265 sh (2.72) and 302 (2.84) nm; m/z: 296 (M^+, 33), 295 (30), 281 (70), 279 (100), 264 (20), 177 (33), 176 (50), 121 (30), 120 (40), 119 (30) and 118 (40); ^{1}H NMR ($CDCl_3$): δ 1.56 (d, J=6 Hz, 3H), 2.28-3.52 (m, 6H), 3.56-4.00 (m, 2H), 3.84 (s, 3H), 6.64 (s, 2H), 7.02 (d, J=6 Hz, 1H), 8.30 (d, J=6 Hz, 1H) and 8.44 (s, 1H). (Calc. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found : C, 72.83; H, 6.72; N, 9.31.)

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