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A NOVEL ONE-POT SYNTHESIS OF SUBSTITUTED 1,4-DIHYDROPYRIDINES AND ITS APPLICATION TO TOTAL SYNTHESIS OF THE ALKALOID ISOALAMARINE FROM ALANGIUM LAMARCKII THW.

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Abstract : A novel method for one pot synthesis of unsymmetrical 3,5-disubstituted and 3,4,5,-trisubstituted 1,4-dihydropyridines has been developed. The first total synthesis of the alkaloid isoalamarine (**1**), involving 3-acetyl-5-carbomethoxy pyridine has been accomplished.

1,4-Dihydropyridines occupy an important position in chemistry and biology. This is exemplified by the well-known hydrogen transferring co-enzyme NADH which is involved in biological oxidation-reduction. Among their physiological properties[1,2], it is interesting to note that a few are well-known calcium antagonists[3]. In addition to their role in biological phenomena 1,4-dihydropyridines have the attracting ability to induce asymmetry[4,5] in organic molecules and have wide applicability as starting materials or intermediates in natural product synthesis[6-9] particularly the alkaloids of pyridine as well as pyridobenzoquinolizine systems.

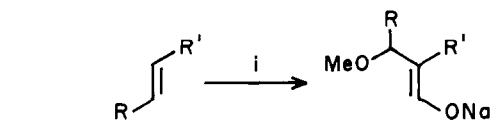
Although a number of syntheses of 1,4-dihydropyridines have been documented in the literature[10-12] no general method covering the synthesis of 3,5-and 3,4,5-unsymmetrically substituted 1,4-dihydropyridines as well as pyridines is known. Hence is the necessity for a simplified procedure to obtain such systems which could form the intermediates for alkaloids.

In the synthetic plan for the total synthesis of the novel alkaloid isoalamarine isolated[13] from the medicinally important plant Alangium lamarckii Thw. it was conceived that 3-acetyl-5-carbomethoxy 1,4-dihydropyridine could be a key synthon for obtaining the substituted pyridine part of the alkaloid.

Many pyridobenzoquinolizine alkaloids[13-15] are built up of a pyridine unit having substituents at 3 and 5 positions. The reported methods[16,17] for preparing 3-acetyl-5-carbomethoxy pyridine involve multiple steps with poor yield. A simple novel one pot methodology has been developed to synthesise the desired intermediate.

Following the same method, it has also been possible to prepare another 3,5-disubstituted and a 3,4,5 trisubstituted 1,4-dihydropyridines with unsymmetrical variants. The methodology involves formylation at the α-position of a α,β-unsaturated Michael acceptor in presence of an alkoxide, followed by condensation with sodioacetoacetaldehyde in presence of ammonia.

Synthesis of 1,4-dihydropyridines : A mixture of sodioacetoacetaldehyde[18] (2) and sodium salt of methyl-2-formyl-3-methoxypropionate[19] (**4a**) was refluxed in ethanol with ammonium acetate, ammonia and acetic acid. Chromatographic purification of the



3

a: R = H, R' = COOMe

b: R = H, R' = CN

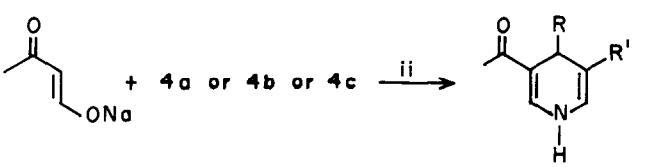
c: R = Me, R' = COOMe

4

a: R = H, R' = COOMe

b: R = H, R' = CN

c: R = Me, R' = COOMe



2

5

a: R = H, R' = COOMe

b: R = H, R' = CN

c: R = Me, R' = COOMe

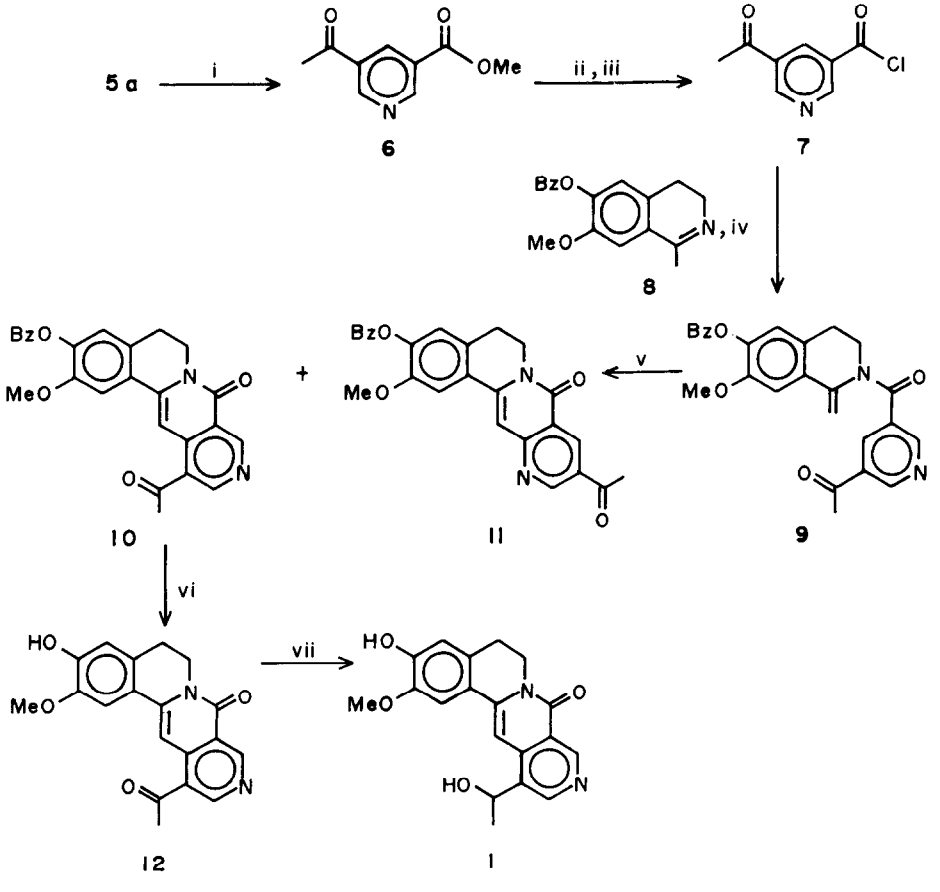
Scheme I. Reagents and conditions: i) NaOMe, HCO_2Et, 0°C

ii) NH_3, NH_4OAc, HOAc, EtOH, 120°, Reflux, 16h.

reaction product afforded 3-acetyl-5-carbomethoxy-1,4-dihydropyridine in 40% yield. In a similar way condensation of **4b** and **4c** separately with **2** yielded 3-acetyl-5-cyano-1,4-dihydropyridine (**5b**) and 3-acetyl-4-methyl-5-carbomethoxy-1,4-dihydropyridine (**5c**) in 45% and 43% yields respectively (**Scheme 1**).

Total synthesis of isoalamarine (1) : The synthesis of isoalamarine (**1**) consists of acylation of 6-benzyloxy-7-methoxy-1-methyl-3,4-dihydroisoquinoline (**8**) with 5-acetylnicotinyl chloride (**7**) followed by thermal cyclisation[20] of the resulting enamide (**9**). For the preparation of 5-acetylnicotinyl chloride, the intermediate 3-acetyl-5-carbomethoxy 1,4-dihydropyridine (**5a**) was oxidised to the corresponding

pyridine (6) with DDQ in almost quantitative yield (96%). The pyridine compound (6) was hydrolysed with aqueous sodium hydroxide and the dry sodio-salt was converted to its acid chloride (7) with oxalyl chloride. The acid chloride (7) was added drop by drop to the ice cooled solution of 6-benzyloxy-7-methoxy-1-methyl-3,4-dihydroisoquinoline (8) in dry benzene in presence of triethylamine at 0° and stirred overnight. The enamide (9) was isolated in almost quantitative amount (96.6%). On thermal cyclisation 9 yielded two isomers 10 (50%) and 11 (10%). After chromatographic separation the desired isomer 10 was debenzylated by refluxing in 50% alcoholic HCl, followed by reduction with sodium borohydride to yield isoalamarine (1) in 18% yield (**Scheme II**). The synthetic compound was found to be identical (TLC, ^{1}H NMR, UV, Mass and IR) with our authentic specimen previously isolated and reported[13] from our laboratory.



Scheme II. Reagents and Conditions: i) DDQ, C_6H_6, Reflux, ii) Aq NaOH, Reflux, 4h. iii) $(COCl)_2$, C_6H_6. iv) Et_3N, C_6H_6, 0°C v) Δ, 180–220°C, Neat, N_2. vi) 50% EtOH/HCl. vii) $NaBH_4$, MeOH.

Following the above methodology the synthesis of naucletine, angustine and angustoline[15] is in progress.

The one – pot methodology has enough scope of generalisation to synthesise different unsymmetrically substituted 1,4-dihydropyridines as well as corresponding pyridines. Varying the two carbon and three carbon participating units in the condensation process to build up the dihydropyridine nucleus it will be possible to bring about desired substitution at 3,4 and 5 positions which was not hitherto possible. The intermediate **5c** is indeed a core unit of different alkaloids and has been an useful synthon for the total synthesis of related natural products.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in a Perkin Elmer Model 177 spectrometer. UV absorptions were observed in a Hitachi U-3200 spectrophotometer. ^1H NMR spectra were measured on a JEOL FX-100 FT NMR spectrometer using TMS as internal standard and $CDCl_3$ or DMSO as solvents. The mass spectra were taken on a Hitachi RMU-6L instrument. Thin layer chromatograms were made with silica gel (SRL). Spots in the TLC plates were developed by iodine and also observed by UV fluorescence. Column chromatographic separations were carried out on neutral alumina (Glaxo).

General reaction procedure for 1,4-dihydropyridines : A representative procedure is illustrated for the compound 3-acetyl-5-carbomethoxy-1,4-dihydropyridine (**5a**). A mixture of methyl acrylate (10.45 g, 0.12 mol) and ethyl formate (17.88 g, 0.24 mol) was added dropwise to powder sodium methoxide (15.90 g, 0.29 mol) under ice cooling with stirring for an hour under N_2 atmosphere. The stirring was continued for another 2.5 h below 10°C to give methyl-2-formyl-3-methoxypropionate as yellow syrup. To it was added sodioacetoacetaldehyde (40 g, 0.37 mol), ammonium acetate (12 g), acetic acid (28 g, 0.46 mol) and lime dried ethanol (600 ml). The mixture was stirred and refluxed at 120°C for 16 h with constant bubbling of ammonia gas. Alcohol was distilled off on a water bath under reduced pressure. The residue was extracted with ethylacetate (3 x 100 ml) and the solvent was distilled off. It was then dissolved in chloroform-methanol (1:1). The material was adsorbed on neutral alumina and subjected to column chromatography. Elution with chloroform-petroleum ether (8:2) yielded solid residue (8.78 g, 40%). A part of the residue was crystallised from chloroform-petroleum ether to yellow needles (**5a**), mp 175-180°C; IR (Nujol mull) : 3125, 1690(br), 1205 cm^{-1}; UV λ_{max}(MeOH) : 227(4.09), 254(3.69), 385(3.90) nm; ^1H NMR (100 MHz, $CDCl_3$) : 2.20(s,3H), 3.24(s, 2H), 3.72(s, 3H), 7.08(s, 1H), 7.14(s, 1H); MS m/z: 181(27, M^+), 166(100), 150(6); Anal. Cal. for $C_9H_{11}NO_3$: C, 59.72; H, 6.13; N, 7.74%. Found : C, 59.43; H, 6.30; N, 7.64%.

3-Acetyl-5-cyano-1,4-dihydropyridine (5b) : The above reaction was performed under identical conditions using acrylonitrile (1.21 g, 0.02 mol), sodium methoxide (5.2 g,

0.09 mol), acetic acid (33 g, 0.55 mol), sodioacetoacetaldehyde (18 g, 0.16 mol), ammonium acetate (6 g), ammonia gas, lime dried ethanol (200 ml). The reaction mixture was worked up as usual and chromatographed over neutral alumina. Elution with chloroform-methanol (98:2) yielded a solid residue (1.59 g, 45%). A part of the residue was crystallised from chloroform-methanol to obtain (**5b**), mp 220°C; IR (Nujol mull): 3150, 2130 (br), cm^{-1}; UV λ_{max} (MeOH): 222.8(4.38), 373.8(4.11) nm ; ^1H NMR(100 MHz), CD_3OD): 2.20(s, 3H), 3.12(s,1H), 6.84(s, 1H), 7.28(s,1H); MS m/z: 148(93, M^+), 132(58), 104(21); Anal. Cal. for $C_8H_8N_2O$: C, 64.90; H, 5. 45; N, 18.93%. Found ; C, 64.5; H, 5.43; N, 18.75%.

3-Acetyl-4-methyl-5-carbomethoxy-1,4-dihydropyridine (5c) : The reaction was also done under similar conditions using methyl crotonate (2.54 g, 0.025 mol), sodium methoxide, (3.56 g; 0.065 mol), sodioacetoacetaldehyde (18.0 g, 0.16 mol), ammonium acetate (6 g), acetic acid (33.0 g, 0.55 mol) ammonia gas, ethanol (200 ml). It was worked up as usual. During chromatographic purification elution with chloroform petroleum ether (9:1) afforded **5c** (2.2 g, 43%), Yellow crystals were obtained from chloroform-petroleum ether, mp 160-162°C ; IR (KBr) : 1695, 1675, 1605, 1505, 1435, 1210 Cm^{-1} ; UV λ_{max}(MeOH) : 227.4(3.99), 370(3.79) nm ; ^1H NMR(100 MHz, $CDCl_3$) : 1.07 (d, J=6Hz, 3H), 2.32(s, 3H), 3.75(s, 3H), 3.96(q, J=7Hz, 1H), 7.14(s, 1H), 7.26(s, 1H); MS m/z : 195(45.1, M^+), 180(100), 164(59), 138(67). Anal. Cal. for $C_{10}H_{13}NO_3$: C, 62.23 ; H, 6.79 ; N, 7.26%. Found : C, 62.02 ; H, 6.50 ; N, 7.02%.

3-Acetyl-5-carbomethoxy pyridine (6) : A mixture of (**3c**) (600 mg, 3.31 mmol) and DDQ (751 mg, 3.30 mmol) was taken in dry benzene (40 ml) and refluxed for 12 h on water bath. The product was purified by passing through a basic alumina bed followed by elution first with chloroform and then chloroform-methanol (9:1). After evaporation of the solvent, the residue was crystallised from chloroform-petroleum ether to yield **6** in 96% yield (575 mg), mp 90°C ; IR (KBr) : 3020, 1715, 1685, 1255, 1235 cm^{-1} ; ^1H NMR (100 MHz, $CDCl_3$) : 2.68(s, 3H), 4.00(s, 3H), 8.80(t, J=2Hz, 1H), 9.34 (d, J=2Hz, 1H), 9.38(d, J=2Hz, 1H) ; MS m/z : 179(51, M^+), 164 (100) 149(35, 137(61).

Preparation of 3-acetyl nicotinyl chloride (7) : Compound **6** (390 mg, 2.18 mmol) was hydrolysed by refluxing with 1.0 N sodium hydroxide solution (2 ml) for 4 h under nitrogen in an oil-bath. The solvent was removed in a rotary evaporator and last traces of moisture by distillation with dry benzene (4 x 2 ml). Oxalyl chloride (5 ml) was added to the above sodium salt in dry benzene (6 ml) at 0-5°C and kept for an hour. It was then refluxed in an oil bath for 1.5 h. Excess oxalyl chloride was removed by fractional distillation and to ensure complete removal it

was fractionally distilled two times with dry benzene.

Preparation of enamide (9) : A solution of isoquinoline base (**8**) (595 mg, 2.12 mmol) and triethylamine (1.12 ml) in dry benzene (24 ml) was cooled in ice bath and kept stirred under N_2 atmosphere. The acid chloride (**7**) in dry benzene (2 ml) was added to this and the reaction mixture was stirred for one hour and left overnight. It was then filtered and the filtrate was extracted with chloroform. The product was purified by fractional crystallisation (881 mg, 96.6%), mp 128°C; IR (KBr) : 3400, 1685, 1625, 1505, 1400, 1255 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) : 2.60 (S, 3H), 2.96 (t, J=7Hz, 2H), 3.88 (s, 3H), 4.12 (t, J=7Hz, 2H), 4.35 (d, J= 2Hz, 1H), 5.16 (s, 2H), 5.30 (d, J= 2Hz, 1H), 6.68 (s, 1H), 7.28-7.60 (m, 5H), 8.32 (t, J = 2Hz, 1H), 8.76 (d, J=4Hz, 1H), 9.12 (d, J= 4Hz, 1H) ; MS m/z; 428 (5, M^+), 309 (8), 281 (12), 268 (2), 190 (16), 91 (100).

Thermal cyclisation of enamide (9) : The enamide (53 mg, 0.124 mmol) was heated neat at 188-220°C for 20 minutes. Chromatographic purification over neutral alumina and elution with petroleum ether-chloroform (4:6) afforded **11** (5 mg, 10.5%). Further elution with chloroform-petroleum ether (7:3) yielded the desired isomer **10** (26.5 mg, 50%).

(**10**) : Orange needles were obtained by crystallisation from chloroform-petroleum ether, mp 210°C ; IR (KBr) : 3400, 1680, 1595, 1515, 1270 cm^{-1} ; UV λ_{max}(MeOH): 260 (4. 71), 375 (4.77) nm ; ^1H NMR (100 MHz, $CDCl_3$) : 2.74 (s, 3H), 2.84 (t, J = 7Hz, 2H), 4.04 (s, 3H), 4.3 (t, J = 7Hz, 2H), 5.20 (s, 2H), 6.79 (s, 1H), 7.24-7.52 (m, 6H), 8.08 (s, 1H), 9.64 (s, 1H); MS m/z : 426 (16.25, M^+), 336 (12.5), 321(6, 8), 307 (5), 221 (6.6).

(**11**) : Crystallisation from chloroform-petroleum ether yielded yellow granules, mp 150°C ; IR (KBr) 1700, 1675, 1640, 1600, 1555, 1515, 1275, 1215 cm^{-1} ; ^1H NMR ($CDCl_3$, 100 MHz), 2.62 (s, 3H), 3.02 (t, J= 7Hz), 3.72 (t, J= 7Hz), 3.88 (s, 2H), 5.16 (s, 1H), 6.84 (s, 1H) 7.22 (s, 1H), 7.24-7.50 (m, 5H), 8.54 (t, 1H), 9.10 (d, J = 4Hz), 9.18 (d, J = 4Hz).

Debenzylation of 10 : Compound **10** (47 mg, 0.11 mmol) was taken in 3 ml of 50% EtOH/HCl and refluxed for 1 h. It was diluted with water (5 ml), extracted with ether and washed with dil. $NaHCO_3$ solution, dried (Na_2So_4) and the solvent evaporated. The residue on crystallisation from methanol-chlorofomy yielded **12** (14.4 mg, 40%) mp> 280°C. IR (KBr) : 1600, 1640, 1270 cm^{-1}, UV λ_{max}(MeOH) : 378.8 (4.3), 304.2 (3.6), 260.8 (4.1), 242.8 (4.04) ; (NaOH) 437.2 (4.38), 324.0 (3.6), 263.4 (4.0), 247.2

(3.9) nm ; ^{1}H NMR (100 MHz, DMSO-d_6) 2.74 (s, 3H), 2.84 (m), 3.88 (s, 3H), 4.18 (t, J= 7Hz), 6.80 (s, 1H), 7.29 (s, 1H), 7.86 (s, 1H), 9.26 (s, 1H), 9.44 (s, 1H); MS m/z : 336 (100, M^+), 321 (82).

Preparation of Isoalamarine (1) : Compound **12** (20 mg ; 0.06 mmol) was treated with $NaBH_4$ (100 mg) in methanol (1 ml). The reaction mixture was decomposed with a drop of acetic acid. Few drops of water were then added and basified with ammonia, extracted with chloroform. The homogeneity of the product was ascertained by TLC. Yield (19 mg, 95%).

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REFERENCES :

1. Ross, W. C. J., J. Chem. Soc., C. 1966, 1816.
2. Marks, G. S. ; Hunter, E. G. ; Terner, U.K. and Schneck, D. ; Biochem. Pharmacol., 1965, 14, 1077.
3. Vater, W. ; Kroneberg, G. ; Hoffmeister, F. ; Kaller, H. ; Meng, K. ; Oberdorf, A.; Puls, W. ; Schlossmann, K. and Stoepel, K., Arzneim-Forsch., 1972, 22, 1.
4. Nishiyama, K. ; Baba, N. ; Oda, J. and Inouye, Y., J. Chem. Soc., Chem. Commun. 1976, 101.
5. Baba, N. ; Nishiyama, K. ; Oda, J. and Inouye, Y., Agric. Biol. Chem., 1976, 40, 1441.
6. Wenkert, E. ; Chang, C. ; Chawla, H. ; Cochran, D. ; Hagaman, E. ; King, J. and Orito, K. J. Am. Chem. Soc., 1976, 98, 3645.
7. Wenkert, E. ; Halls, T. ; Kunesch, G. ; Orito, K. ; Stephens, R. ; Temple W. and Jadav, J. Ibid., 1979, 101, 5370.
8. Naito, T.; Miyata, O. and Ninomiya, I.; J. Chem. Soc., Chem. Commun. 1979, 517.

9. Lounasmaa, M. ; Juutinen, P. and Kairisalo, P., Tetrahedron, 1978, 34, 2529.

10. Eisner, U. and Kuthan, J. ; Chem. Rev., 1972, 72, 1.

11. Stout, D. M. and Meyers, A.I. ; ibid, 1982, 82, 223.

12. Sausiņš, A. and Dubur, G. ; Heterocycles, 1988, 27, 269.

13. Pakrashi, S.C. ; Mukhopadhyay, R. ; Sinha, R.R. ; Ghosh Dastidar, P.P. ; Achari, B. and Ali, E. Ind. J. Chem., 1985, 24B, 19.

14. Pakrashi, S.C. ; Achari, B.; Ali E. ; Ghosh Dastidar, P.P. and Sinha, R.R. ; Tetrahedron Lett., 1980, 21, 2667.

15. Au, T.Y. ; Cheung, H.T. and Sternhell, S. ; J. Chem. Soc., Perkin. 1, 1973, 13.

16. Kuthan, J. and Paleček, J. ; Coll. Czeck. Chem. Comm., 1966, 31, 2618.

17. Lukeš, R. and Vaculík, P. ; Chem. Listy, 1957, 51, 1510.

18. Lipinski, C.A. ; Blizniak, E. and Craig, R.H. ; J. Org. Chem., 1984, 49, 566.

19. Tanaka, M. ; Kimoto, M. and Tokuyama, K. ; Chem. Pharm. Bull., 1978, 26, 38.

20. Naito, T. ; Miyata, O. ; Ninomiya, I. and Pakrashi, S.C. ; Heterocycles, 1981, 16, 725.