SYNTHESIS OF THE ALKALOIDS (±)-NORMALINDINE AND (±)-NORISOMALINDINE

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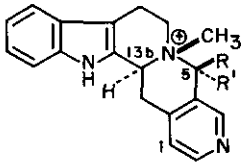
Abstract - The alkaloids normalindine (3) and norisomalindine (4) have been synthesised via the β-carbolinium salt (7) by pivaloyl chloride induced cyclization and subsequent reduction with sodium cyanoborohydride.

A number of indole alkaloids containing the indolopyridoquinolizine ring system have been isolated[1] and synthesised[2,3] over the past few years. However, all of them are lactams. More recently, the alkaloids malindine (1),[4] isomalindine (2),[5] normalindine (3) and norisomalindine (4)[6] with an unusual methyl substituent at C-5 have been encountered in nature. Earlier, we reported from this laboratory the synthesis[7] of alamaridine, the benzo analogue of this class of alkaloids. Herein we describe the first total synthesis of (±)-normalindine and (±)-norisomalindine following similar procedure.

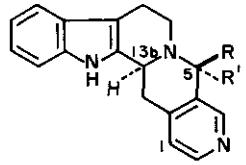
The readily accessible imine (5) on $NaBH_4$ reduction in methanol at room temperature followed by acetylation gave the amide (6) [79%, mp 130-132°C; ir (KBr): 3180 (NH), 1610 (NCO) cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.59 (3H, d), 2.20 (3H, s), 5.98 (1H, q); ms (M^+, 307)] which on cyclization with $POCl_3$ afforded β-carbolinium salt (7), isolated as its bisperchlorate [73%; mp >300°C (dec.); ^{1}H-nmr (DMSO-d_6): δ 1.92 (d, 3H), 3.04 (s, 3H), 6.08 (q, 1H)]. The required cyclization to the pentacyclic system was brought about by pivaloyl chloride - Et_3N presumably through the intermediacy of a dihydropyridine system which underwent spontaneous oxidation to dehydronormalindine (8) [30%; mp 235-237°C; uv (log ε): λ_{max} (MeOH) 310 (3.94), 410 nm (4.12); ^{1}H-nmr ($CDCl_3$): δ 1.32 (d, 3H), 4.64 (q, 1H), 5.60 (s, 1H, H-14); ms (M^+, 287). Reduction of 8 with $NaBH_3CN$ in acetic acid at 5-10°C yielded a diastereoisomeric mixture of 3 (55%) and 4 (6%). The ^{1}H-nmr of the major isomer exhibited a methyl doublet at δ 1.62 and a methine quartet at δ 3.84. On the other hand, the same signals for the minor product appeared at δ 1.42 and 4.40 respectively with an additional double doublet at δ 4.34. The presence of Bohlmann bands in the major isomer and their absence in the minor compound along with their ^{1}H-nmr data confirm the trans and cis quinolizine ring systems for them respectively (cf. 8-methyltetrahydroprotoberberine system[8,9]). Thus, the structure and the stereochemistry at C-5 and C-13b in normalindine (3) and norisomalindine (4) are established. The compounds were found to be identical (tlc, uv, ir, ^{1}H-nmr, ms) to the natural ones.

EXPERIMENTAL

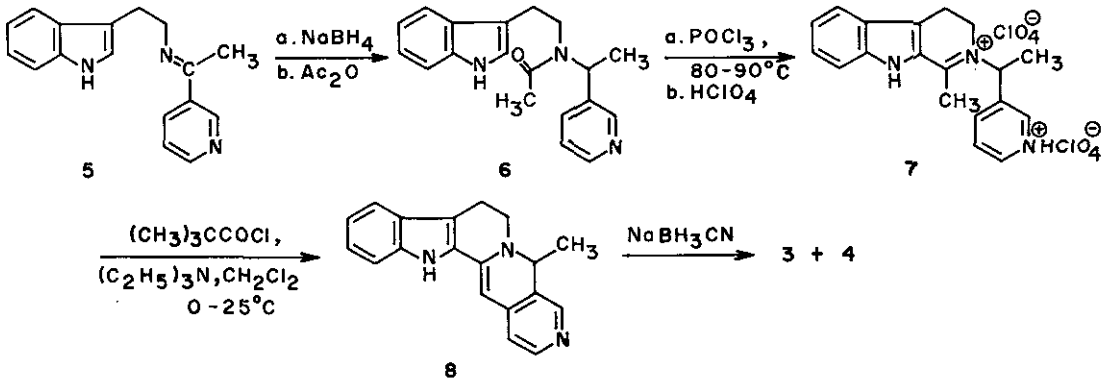
Mps, taken in open capillaries, are uncorrected, ir spectra recorded in a Perkin-Elmer 177



1. R = CH_3, R' = H, malindine
2. R = H, R' = CH_3, isomalindine



3. R = CH_3, R' = H, normalindine
4. R = H, R' = CH_3, norisomalindine



infrared spectrophotometer; ^{1}H-nmr spectra were measured in a JEOL FX-100 FT nmr spectrometer using TMS as internal standard and the mass spectra (EI) were taken on a Hitachi RMU-6L instrument.

N-1-(3'-Pyridyl)ethyltryptamine

A solution of tryptamine (4 g, 25 mmol) and 3-acetylpyridine (3.65 g, 30 mmol) in dry benzene-alcohol (80 ml, 9:1) was refluxed for 48 h using a Dean-Stark apparatus. The solvent was removed under reduced pressure and the residual oil (5) was dried under vacuum. To a solution of the residue in methanol (25 ml) was added $NaBH_4$ (0.75 g, 20 mmol) 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 (50 ml) and extracted with $CHCl_3$ (3 x 50 ml). The organic phase was washed successively with water and brine, dried over anhydrous Na_2SO_4 and evaporated to yield an oil (7.5 g). It was chromatographed over neutral alumina to give N-1-(3'-pyridyl)ethyltryptamine as an oil (6.3 g, 94%), ir ν_{max} (neat); 3400, 3200 and 1590 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.32 (d, J = 7 Hz, 3H), 2.70-3.12 (m, 4H), 3.80 (q, J = 7 Hz, 1H), 7.00 (br s, 1H), 7.04-7.40 (m, 4H), 7.48-7.80 (m, 2H), 8.12 (br s, 1H) and 8.40-8.60 (m, 2H); ms m/z (rel. intensity) : 265 (M^+, 20), 179 (14), 164 (30), 159 (25), 135 (90), 130 (100) and 106 (98).

N-Acetyl-N-1-(3'-pyridyl)ethyltryptamine (6)

A solution of the above amine (7.95 g) was treated with acetic anhydride (20 ml) at 0°C and then kept at room temperature for 24 h. The reaction mixture was poured into ice water (200 ml) and extracted with $CHCl_3$ (3 x 100 ml). The organic phase was washed with water, dried over anhydrous Na_2SO_4 and finally concentrated to yield an oil which was then chromatographed over neutral alumina. Elution with $CHCl_3$ gave an oil which was crystallised from chloroform-petroleum ether to afford 7.3 g (79%) white granules of **6**, mp 130-132°C; ir ν_{max} (KBr); 3180, 1610 and 1420 cm^{-1}; uv (log ϵ): λ_{max} (MeOH) 223 (4.63), 268 (3.85), 280 (3.81) and 288 nm (3.79); ^{1}H-nmr ($CDCl_3$): δ 1.59 (d, J = 7 Hz, 3H), 2.20 (s, 3H), 2.50-3.04 (m, 2H), 3.20-3.62 (m, 2H), 5.98 (q, J = 7 Hz, 1H), 6.84 (br s, 1H), 7.10-7.44 (m, 5H), 7.68 (t, J = 8 Hz, 1H), 8.24 (br s, 1H) and 8.56-8.64 (m, 2H); ms m/z (rel. intensity): 307 (M^+, 14), 165 (90), 144 (71), 143 (82), 130 (95) and 106 (100); Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.33; H, 6.90; N, 13.69. Found : C, 73.96; H, 6.82; N, 13.28.

1-Methyl-2-[α-(3'-pyridyl)ethyl-3,4-dihydro-β-carbolinium bisperchlorate (7)

A suspension of the amide (**6**) (6.1 g) in $POCl_3$ (30 ml) was heated at 80-90°C with stirring. During heating the amide (**6**) dissolved and another solid appeared after 1 h and the heating was continued for 3 h. Excess $POCl_3$ was removed under reduced pressure and the residual solid after drying under vacuum was taken in methanol (20 ml) and cooled in ice water. To this was added a solution of 60% $HClO_4$ (2 ml). The precipitated salt was filtered, washed with ethanol followed by ether and dried under vacuum to afford 7.2 g (73%) of bisperchlorate (**7**), mp > 300°(dec.); uv (log ϵ): λ_{max} (MeOH) 252 (3.97) and 362 nm (4.23); ^{1}H-nmr (DMSO-d_6): δ 1.92 (d, J = 6 Hz, 3H), 3.04 (s, 3H), 3.00-3.20 (m, 2H), 3.50-4.08 (m, 2H), 6.08 (q, J = 6 Hz, 1H), 6.92-7.86 (m, 4H), 8.08 (dd, J = 8,6 Hz, 1H), 8.64 (d, J = 8.0 Hz, 1H), 8.64 (d, J = 8 Hz, 1H), 8.88 (d, J = 6 Hz, 1H), 8.92 (s, 1H) and 12.40 (s, 1H); Anal. Calcd for $C_{19}H_{21}Cl_2N_3O_8$: C, 46.53; H, 4.28; N, 8.57. Found : C, 46.38; H, 4.21; N, 8.64.

Dehydronormalindine (8)

A suspension of the salt (**7**) (4.9 g, 10 mmol) in CH_2Cl_2 (100 ml) was treated with Et_3N (2 ml) at 0°C. To the resulting brown solution pivaloyl chloride (1.32 g, 11 mmol) in CH_2Cl_2 (5 ml) was added at 0°C with stirring and the reaction mixture was kept at 30°C for 2 h. The deep red reaction mixture was concentrated and chromatographed over basic alumina. Elution with chloroform afforded **8** (0.88 g, 30%), mp 235-237°C; ir ν_{max} (nujol) 3400 and 1580 cm^{-1}; uv (log ϵ): λ_{max} (MeOH) 310 (3.94) and 410 nm (4.12); ^{1}H-nmr ($CDCl_3$): δ1.32 (d, J = 7 Hz, 3H), 2.96-3.16 (m, 2H), 3.40-3.70 (m, 2H), 4.64 (q, J = 7 Hz, 1H),

5.60 (s, 1H), 6.80-7.68 (m, 4H), 7.74 (d, J = 7 Hz, 1H), 8.08 (s, 1H), 8.18 (d, J = 7 Hz, 1H) and 8.44 (br s, 1H); ms m/z (rel. intensity) : 287 (M^+, 18), 272 (100) and 134 (90); Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.51; H, 5.97; N, 14.64. Found : C, 79.10; H, 6.01; N, 14.33.

Normalindine (3) and norisomalindine (4)

To a solution of dehydronormalindine (8) (2.87 g, 10 mmol) in glacial acetic acid (10 ml) at 5-10°C was added in portions $NaBH_3CN$ (4 x 50 mg, 3.3 mmol). The reaction was monitored by tlc and after the complete disappearance of deep fluorescence (2 h), water (100 ml) was added to the reaction mixture and the excess acid was neutralised with solid Na_2CO_3. It was extracted with chloroform (3 x 50 ml), washed successively with water, brine, dried over anhydrous Na_2SO_4 and concentrated to afford a gummy residue (2.1 g). Tlc of this residue showed it to be a mixture of 3 and 4 which was purified and separated by preparative tlc on silica gel using ethyl acetate saturated with ammonia vapour. The compound with higher R_f value was found to be 3 (1.6 g, 55%), mp 196-198°C; ir ν_{max} (KBr): 3180, 2740-2840 (Bohlmann bands), 1590 cm^{-1}; uv (log ε): λ_{max} (MeOH) 223 (4.07) and 268 nm (3.43); ^{1}H-nmr ($CDCl_3$): δ 1.62 (d, J = 7 Hz, 3H, CH-CH_3), 2.40-3.16 (m, 6H), 3.50-3.70 (m, 1H), 3.84 (q, J = 7 Hz, 1H, C$\underline{H}$-CH_3), 7.00-7.40 (m, 4H, Ar-H), 7.46 (m, 1H, H-1), 7.96 (br, 1H, NH), 8.36 (d, J = 9 Hz, 1H, H-2) and 8.50 (s, 1H, H-4); ms m/z (rel. intensity): 289 (M^+, 97), 288 (69), 274 (100), 245 (22) and 169 (78); Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.96; H, 6.63; N, 14.54. Found : C, 78.76; H, 6.55; N, 14.28. The slower moving one was identified as 4 (180 mg, 6%), mp 114-117°C; ir ν_{max} (KBr): 3200 (NH) and 1595 cm^{-1}; uv (log ε): λ_{max} (MeOH) 224 (4.29) and 269 (3.63); ^{1}H-nmr ($CDCl_3$): δ 1.42 (d, J = 7 Hz, 3H, CH-CH_3), 2.60-3.20 (m, 6H), 4.34 (dd, J = 12,7 Hz, 1H, H-13b), 4.40 (q, J = 7 Hz, 1H, C$\underline{H}$-CH_3), 7.00-7.40 (m, 4H, Ar-H), 7.56 (d, J = 9 Hz, 1H, H-1), 8.00 (br, 1H, NH), 8.36 (d, J = 9 Hz, 1H, H-2) and 8.40 (s, 1H, H-4); ms m/z (rel. intensity): 289 (M^+, 97), 288 (69), 274 (100), 245 (22) and 169 (78); Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.96; H, 6.63; N, 14.54. Found : C, 78.88; H, 6.51; N, 14.26.

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