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SYNTHESIS OF THE ALKALOID NAUCLEFIDIN

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Abstract: Synthesis of the alkaloid nauclefidine (**1**) through the intermediacy of the quinolizine **4** is described. McFadyen-Stevens reaction of the corresponding tosyl hydrazide (**6**) of **4** afforded **1**.

Nauclefidine (**1**) is an indole alkaloid from *Nauclea officinals*[1], a plant reported to have been widely used as an anti-inflammatory and anti-bacterial agent in China. The structure of the alkaloid has recently been revised and synthetically confirmed[2]. We have now synthesized the alkaloid (**1**) by a simple procedure (Scheme 1) in better yield. This involves condensation of 1-methyl-3,4-dihydro-β-carboline (**2**)[3] and dimethyl methoxymethylenemalonate (**3**)[4] in dry methanol at room temperature to afford 3-carbomethoxy-4-oxo-6,7-dihydroindolo[2,3-a] quinolizine (**4**) in 94% yield. **4** was heated with hydrazine hydrate in DMF at 80-85^{0}C for 2 h. The hydrazide **5** obtained in near quantitative yield was treated with

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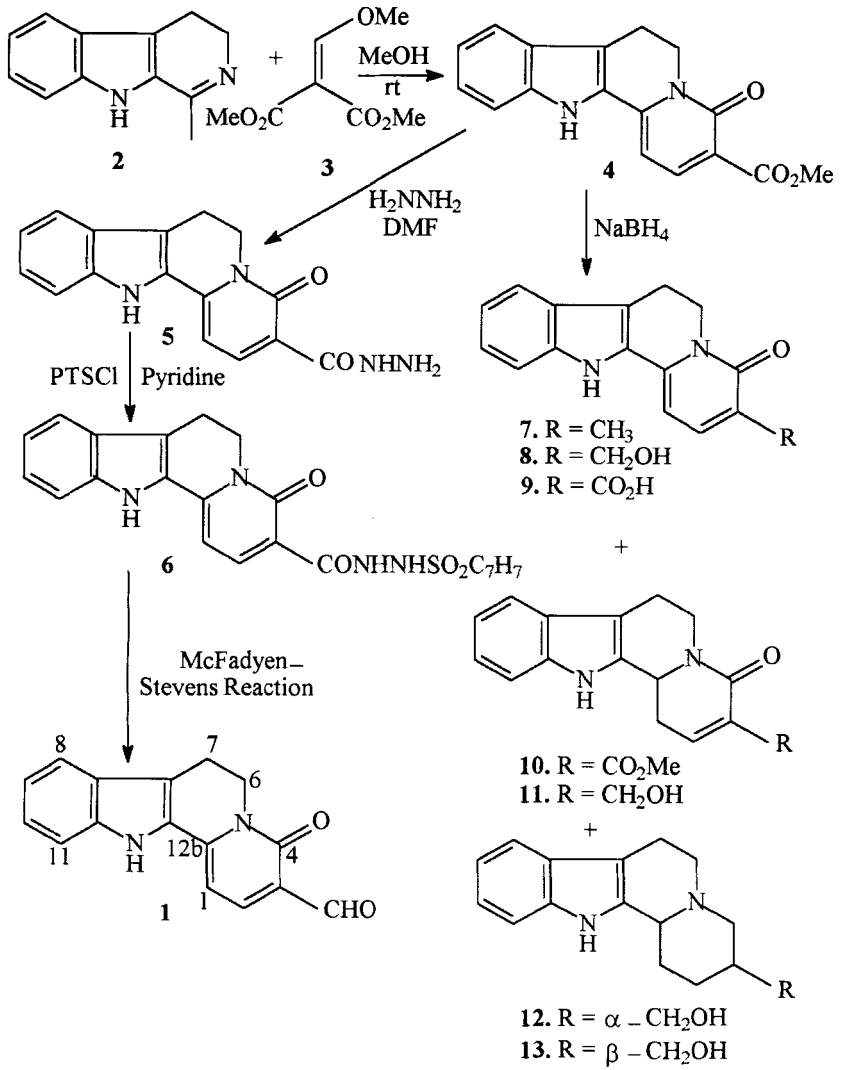

Scheme 1

PTSCl in pyridine at room temperature for 2 h. to afford the tosyl hydrazide **6** in excellent yield. Mcfadyen-Stevens reaction of **6** resulted in the alkaloid nauclefidine (**1**). The physical data of the compound is in agreement with those reported in the literature[2]. Usual $NaBH_4$ reduction of **4** in methanol at room temperature for 3 h.

afforded a mixture of compounds **8**, **9**, **10**, **11**, **12** and **13** although quenching of the reaction mixture with dil. HOAc 10 min. after addition of $NaBH_4$ to **4** resulted in the formation of only one compound **10** (a Michael acceptor) in 5%, the rest being the starting material. Reduction of **4** with $NaBH_4$ in dioxane-water (1:1) afforded alcohol **8** as the major product (50%) along with **7**, **9**, **10**, **11**, **12** and **13** in varying proportions. All the compounds have been charecterised from their physical data.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a JASCO-700 spectrophotometer. NMR spectra were measured on a JEOL FX-100 FT or VARIAN 200 MHz spectrometer using TMS as internal standard and the mass spectrum were recorded on a JEOL AX-500 spectrometer at 70 eV. Petroleum ether refers to the fraction boiling in the range 60-80^{0}C. The known compounds **2**[3] and **3**[4] were obtained following literature procedures.

3-Carbomethoxy-4-oxo-6,7-dihydroindolo[2,3-a]quinolizine (4)

184 mg (1 mmol) of 1-methyl-3,4-dihydro-β-carboline (**2**) was added to a solution of 190 mg (1.1 mmol) of dimethyl methoxymethylenemalonate (**3**) in dry methanol (15 ml). The solution was stirred for 8 h. at room temperature. The solid formed was filtered, washed with methanol and dried (210 mg). The mother liquor on concentration afforded another 66 mg of the same solid. It was recrystallised from methanol-chloroform and characterised as 3-carbomethoxy-4-oxo-6,7-dihydro indolo[2,3-a]quinolizine (**4**); mp 299-300^{0}C; IR: 3308, 1713, 784, 729 cm^{-1}; ^{1}H

NMR (200 MHz; DMSO-d_6): δ 3.08 (t, J=7.5 Hz, 2H), 3.75 (s, 3H), 4.30 (t, J=7.5 Hz, 2H), 6.80 (d, J=7 Hz, 1H), 7.10 (t, J=7 Hz, 1H), 7.30 (t, J=7 Hz, 1H), 7.45 (d, J=7 Hz, 1H), 7.63 (d, J=7 Hz, 1H), 8.13 (d, J=7 Hz, 1H), 11.85 (s, 1H, N*H*); MS m/z (rel. int.): 294 (M^+, 100), 261 (93), 234 (45), 206 (46), 97 (34), 91 (68); Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.45; H, 4.80; N, 9.53. Found: C, 69.29; H, 4.86; N, 9.44.

4-Oxo-6,7-dihydroindolo[2,3-a]quinolizin-3-carbohydrazide (5)

Hydrazine hydrate (0.6 ml) was added to a solution of 294 mg of compound **4** in DMF (5 ml) and the mixture was heated at 80-85°C for 2 h. The mixture was diluted with methanol and the solid formed was filtered. It was recrystallised from methanol to obtain **5** (270 mg; 92%): mp 290-292°C; IR: 3252, 1661, 780, 739 cm^{-1} MS m/z (rel. int.): 294 (M^+, 32), 279 (57), 263 (100), 235 (15), 205 (30), 154 (13).

4-oxo-6,7-dihydroindolo[2,3-a]quinolizin-3-*p*-tolunesulphonyl carbohydrazide (6)

To a pyridine (3 ml) solution of compound **5** (294 mg; 1 mmol), *p*-toluene sulphonyl chloride (210 mg; 1mmol) was added under stirring. The reaction mixture became clear after 5 min. and the stirring was continued for 2 h more. Excess pyridine was removed in a rotavapor, the residue diluted with water and the solid was filtered. It was thoroughly washed with water, dried (385 mg; 94%) and recrystallised from methanol to obtain **6**: mp 302-303°C; IR: 3334, 1659, 740 cm^{-1}; ^1H NMR (200 MHz; DMSO-d_6): δ 2.35 (s, 3H), 3.10 (t, J=7.1 Hz, 2H), 4.40 (t, J=7.1 Hz, 2H), 6.85 (d, J=7.8 Hz, 1H), 7.05 (t, J=7 Hz, 1H), 7.20 (t, J=7 Hz, 1H),

7.25 (d, J=8 Hz, 1H), 7.35 (d, J=8 Hz, 1H), 7.55 (d, J=8 Hz, 1H), 7.70 (d, J=8 Hz, 2H), 8.15 (d, J=7.8 Hz, 1H), 9.70 (s, 1H), 11.20 (s, 1H), 11.65 (s, 1H); MS m/z (rel. int.): 448 (M^+, 10), 293 (13), 279 (46), 263 (100), 235 (98), 206 (38), 156 (24); Anal. Calcd. for $C_{23}H_{20}N_4O_4S$: C, 61.66; H, 4.50; N, 12.51. Found: C, 61.48; H, 4.40; N, 12.38.

Nauclefidine (1)

Aryl hydrazide **6** (112 mg; 0.25mmol) was mixed with powdered glass (100 mg), anhydrous Na_2CO_3 (15 mg) and ethylene glycol (3 ml). The mixture was heated at 170^{0}C in an oil bath under nitrogen atmosphere for 10 mins. It was then immediately cooled using ice bath and diluted with water.The mixture was filtered using little $CHCl_3$ (15 ml). The filtrate was extracted twice with chloroform, the extract was dried (Na_2SO_4), concentrated and the residue purified over silica gel column to afford **1** (54 mg; 82%) which was recrystallised from petroleum ether-chloroform as pale brown needles: mp 307-308^{0}C; IR: 3228, 1688, 1630, 737 cm^{-1}; ^{1}H NMR (200 MHz; DMSO-d_6): δ 3.10 (t, J=7.2 Hz, 2H), 4.35 (t, J=7.2 Hz, 2H), 6.80 (d, J=7.7 Hz, 1H), 7.05 (t, J=7.5 Hz, 1H), 7.25 (t, J=7.5 Hz, 1H), 7.40 (d, J=8.1 Hz, 1H), 7.60 (d, J=8.1 Hz, 1H), 7.95 (d, J=7.7 Hz, 1H), 10.10 (s, 1H,-C*H*O), 11.80 (s, 1H, N*H*); MS m/z (rel. int.): 264 (M^+, 63), 236 (98), 235 (100), 206 (26), 180 (10); Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.79; H, 4.58; N, 10.61. Found: C, 72.33; H, 4.70; N, 10.50.

$NaBH_4$ reduction of compound 4 in methanol.

$NaBH_4$ (312 mg; 8 mmol) was added in portions under stirring to a methanolic

solution (10 ml) of compound **4** (294 mg; 1 mmol) at room temperature and the reaction mixture stirred for 3 h. Excess $NaBH_4$ was destroyed with dilute HOAc and the reaction mixture extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), concentrated and then chromatographed over silica gel column using petroleum ether-$CHCl_3$, $CHCl_3$ and then $CHCl_3$-MeOH mixtures of increasing polarity to afford the compounds **8** (1.5%), **9** (1%), **10** (10%), **11** (3%), **12** (45%) and **13** (5%).

$NaBH_4$ reduction of compound 4 in dioxane-water.

$NaBH_4$ (312 mg; 8 mmol) was added in portions under stirring to a dioxane-water (1:1) solution (20 ml) of compound **4** (294 mg; 1 mmol) at room temperature and the reaction mixture stirred for 3 h. The workup as well as the chromatography procedure were done as was followed for the one in methanol resulting in **7** (2%), **8** (50%), **9** (7%), **10** (15%), **11** (8%), **12** (10%) and **13** (3%).

Compound 7: mp 285-286^{0}C(dec.); IR: 3186, 1643, 729 cm^{-1}; ^{1}H NMR (200 MHz; DMSO-d_6): δ 2.05 (s, 3H), 3.00 (t, J=7.5 Hz, 2H), 4.30 (t, J=7.5 Hz, 2H), 6.57 (d, J=7.5 Hz, 1H), 7.00 (t, J=7.4 Hz, 1H), 7.15 (t, J=7.4 Hz, 1H), 7.30 (d, J=8 Hz, 1H), 7.35 (d, J=8 Hz, 1H), 7.50 (d, J=7.5 Hz, 1H), 11.45 (brs, 1H, N*H*); MS m/z (rel. int.): 250 (M^+, 84), 249 (100), 235 (12), 219 (15), 125 (33).

Compound 8: mp 215-217^{0}C; IR: 3242, 1645, 737 cm^{-1}; ^{1}H NMR (100 MHz; DMSO-d_6): δ 3.04 (t, J=7.5 HZ, 2H), 4.32 (t, J=7.5 Hz, 2H), 4.40 (d, J=7.6 Hz, 2H), 5.04 (t, J=6 Hz, 1H, O*H*), 6.76 (d, J=7.9 Hz, 1H), 7.00 -7.60 (m, 4H), 11.64

(brs, 1H, N*H*); MS m/z (rel. int.): 266 (M^+, 21), 265 (100), 248 (36), 237 (72), 219 (33).

Compound 9: mp 281-282^{0}C (dec.); IR: 3180, 1708, 794 cm^{-1}; ^{1}H NMR (100 MHz; DMSO-d_6): δ 3.20 (t, J=7.5 Hz, 2H), 4.40 (t, J=7.9 Hz, 1H), 7.04 (d, J=7.9 Hz, 1H), 7.10-7.80 (m, 4H), 8.44 (d, J=7.9 Hz, 1H), 12.04 (s, 1H, N*H*), 14.56 (s, 1H, COO*H*); MS m/z (rel. int.): 280 (M^+, 45), 279 (100), 260 (80), 236 (98), 235 (98), 206 (80), 205 (68), 91 (65).

Compound 10: mp 220-222^{0}C; IR: 3330, 1741, 1664, 738 cm^{-1}; ^{1}H NMR (100 MHz; $CDCl_3$): δ 2.48-3.08 (m, 4H), 3.68 (dd, J=8.5, 7 Hz, 1H), 3.80 (s, 3H), 4.14 (t, J=7 Hz, 2 Hz), 5.52 (t, J=5 Hz, 1H), 7.04-7.66 (m, 4H), 8.08 (brs, 1H, N*H*); MS m/z (rel. int.) : 296 (M^+, 95), 239 (98), 238 (100), 236 (52), 207 (25), 167 (30), 118 (45).

Compound 11: mp 172-174^{0}C; IR: 3324, 1668, 1634, 773 cm^{-1}; ^{1}H NMR (100 MHz; DMSO-d_6): δ 2.30-2.50 (m, 2H), 2.84 (t, J=7 Hz, 2H), 3.40-3.96 (m, 4H), 4.08-4.36 (m, 1H), 4.64 (t, J=7 Hz, 1H, O*H*), 5.86 (t, J=5 Hz, 1H), 6.94-7.60 (m, 4H), 11.28 (brs, 1H, N*H*); MS m/z (rel. int.): 268 (M^+, 95), 249 (18), 238 (100), 223 (10), 195 (15), 167 (15), 119 (18).

Compound 12: mp 238-240^{0}C; IR: 3236, 1465, 734 cm^{-1}; ^{1}H NMR (100 MHz; DMSO-d_6): δ 0.98-1.60 (m, 2H), 1.60-2.20 (m, 2H), 2.20-2.40 (m, 1H), 2.56-2.80 (m, 2H), 2.80-3.20 (m, 4H), 3.22-3.52 (m, 2H), 4.44 (t, J=5 Hz, 1H), 6.84-7.18

(m, 2H), 7.20-7.58 (m, 2H), 10.64 (s, 1H, N*H*); MS m/z (rel. int.): 256 (M^+, 78), 255 (100), 225 (18),184 (13),170 (32),169 (37),156 (18).

Compound 13: mp 120-122^{0}C; IR: 3164, 1452, 734 cm^{-1}; ^{1}H NMR (100 MHz; DMSO-d_6): δ 1.40-1.96 (m, 3H), 1.98-2.16 (m, 1H), 2.30-3.16 (m, 6H), 3.16-3.80 (m, 3H), 4.20 (brs, 1H, O*H*), 6.80-7.18 (m, 2H), 7.20-7.60 (m, 2H), 10.64 (s, 1H, N*H*); MS m/z (rel. int.): 256 (M^+, 66), 255 (100), 225 (28), 184 (12), 170 (30), 156 (15).

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