SYNTHESIS OF THE ALKALOIDS (±)-DEPLANCHEINE AND FLAVOPEREIRINE

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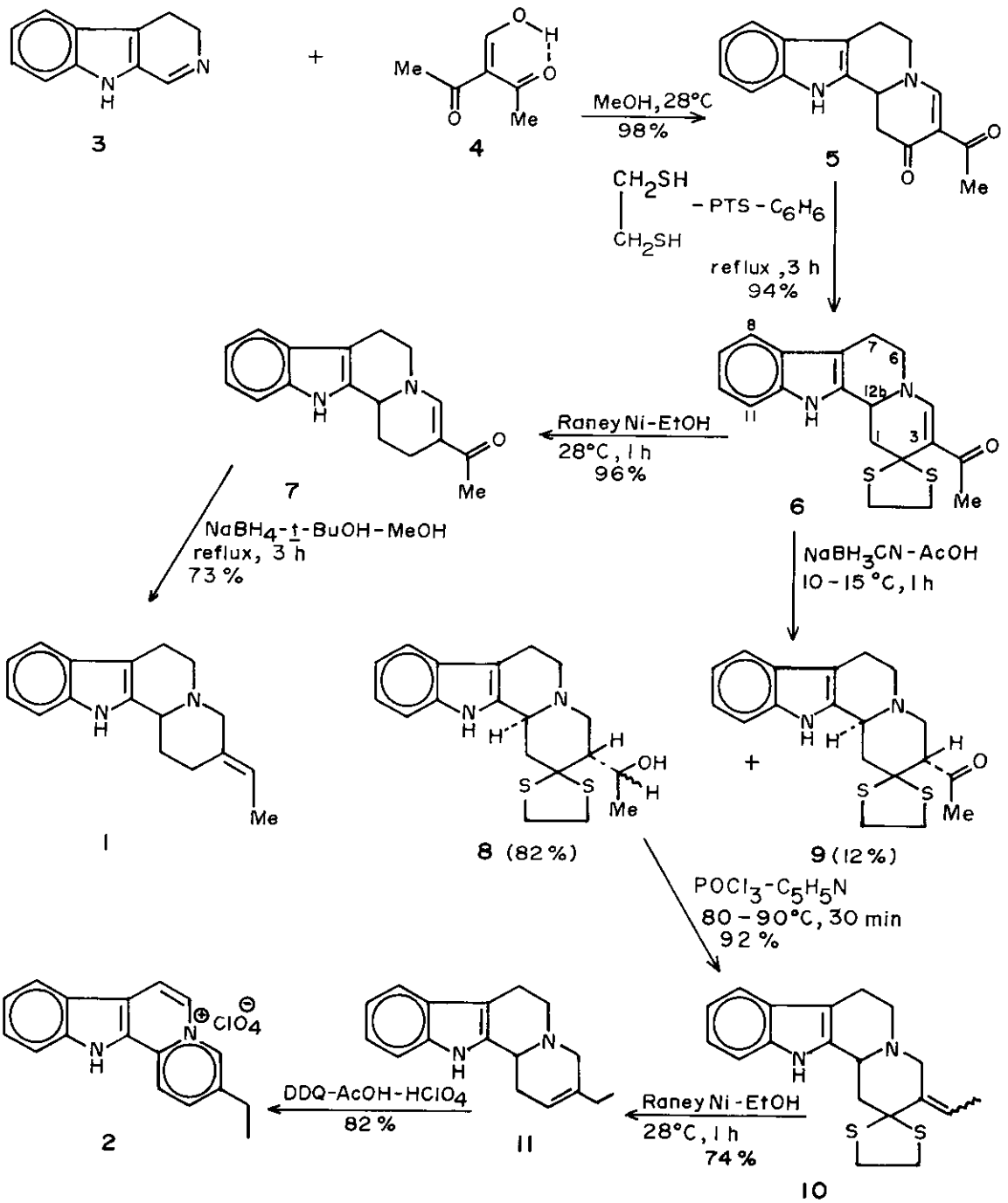
Abstract - Desulfurization of 3-acetyl-1,2,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine-2-ethylene thioketal (6) followed by $NaBH_4$ reduction afforded (±)-deplancheine (1) whereas $NaBH_3CN$ reduction followed by dehydration, desulfurization and DDQ oxidation yielded flavopereirine (2).

The indole alkaloids deplancheine (1),[1] having only an ethylidene side chain with E-configuration at C-3 in an octahydroindolo[2,3-a]quinolizine system, and flavopereirine (2),[2] inhibitor of *in vitro* synthesis of cancer DNA, have been synthesised by different groups in moderate to poor yield. In our ongoing project concerned with the preparation of potential intermediates for indole alkaloid synthesis, it was conceived that 3-acetyl-1,2,6,7,12,12b-hexahydroindolo[2,3-a]quinolizin-2-one (5)[3] could be an ideal intermediate for obtaining alkaloids (1) and (2).

The compound (5) has now been prepared in quantitative yield and at a much faster rate *via* an improved procedure by condensing 3,4-dihydro-β-carboline (3) with hydroxymethyleneacetylacetone (4).[4] Thioketalization of 5 with 1,2-ethanedithiol and PTS in refluxing benzene gave only the thioketal (6), desulfurization of which with Raney Ni in ethanol resulted in the known vinylogous amide (7)[5] in good yield. The regioselective thioketalization may be explained as follows. Delocalization of the system involving lone pair of nitrogen at N-5, double bond between C-4 and C-3 and the carbonyl of the acetyl group would result in less strain compared to the one arising out of coplanarity of N-5, C-4, C-3 and C-2 (>C=O) moiety, thus making the ring carbonyl vulnerable to the reaction. Reduction of 7 with $NaBH_4$ in t-BuOH-MeOH under reflux gave only (±)-E-deplancheine (1) in 73% yield along with some starting material (20%). Stereoselective reduction of similar systems are known[6] and explained on the basis of steric interaction between the H-4 and


3
4
MeOH, 28°C
98%
5
CH2SH
CH2SH
- PTS - C6H6
reflux, 3 h
94%
6
Raney Ni-EtOH
28°C, 1 h
96%
7
NaBH4-t-BuOH-MeOH
reflux, 3 h
73%
NaBH3CN-AcOH
10-15 °C, 1 h
1
8 (82%)
9 (12%)
POCl3-C5H5N
80-90°C, 30 min
92%
10
Raney Ni-EtOH
28°C, 1 h
74%
11
DDQ-AcOH-HClO4
82%
2

the ethylidene methyl group in the iminium salt with Z-configuration being greater than that in the E-iminium salt [Earlier, we have reported[1b] the above reduction in 1,4-dioxane].

$NaBH_3CN$ reduction of the thioketal (6) in AcOH afforded on the other hand only a single diastereoisomeric alcohol (8) (82%) besides the reduced ketone (9) (12%). This high stereoselectivity may be explained by assuming prior reduction of the intermediate iminium functionality followed by stereoselective protonation at C-3 from the β-face assisted by the lone pair of N-5. Dehydration of 8 with $POCl_3$-pyridine gave the olefin (10) in good yield. Desulfurization of 10 with Raney Ni in ethanol resulted in the isomerised compound (11), the ^{1}H-nmr of which showed a characteristic triplet at δ 1.06, a quartet at δ 2.02, and a multiplet at δ 5.54 for the endocyclic vinyl ethyl moiety. Finally, oxidation of 11 with DDQ in AcOH gave flavopereirine (2) [confirmed by direct comparison with authentic sample synthesised by us[2b] previously].

EXPERIMENTAL

Mps taken in open capillaries are uncorrected, ir spectra recorded in a Perkin-Elmer 177 spectrophotometer, ^{1}H and ^{13}C-nmr spectra were measured on a JEOL FX-100FT nmr spectrometer using TMS as internal standard and the mass spectra (EI) were taken on a Hitachi RMU-6L instrument.

Hydroxymethyleneacetylacetone (4)

Acetylacetone (52 ml, 0.5 mol), triethyl orthoformate (84 ml, 0.5 mol), and acetic anhydride (80 ml) were mixed, refluxed for 3 h and then cooled. Water (20 ml) was added, the reaction mixture was again heated to reflux for 5 min and then cooled. The excess acetic acid was removed under reduced pressure and the residue on Claisen distillation yielded 4 (57.2 g, 90%) as colorless hard crystals, mp 42-43°C; bp 60-62°C/0.3 torr (lit.,[4] mp 40-42°C).

3-Acetyl-1,2,6,7,12,12b-hexahydroindolo[2,3-a]quinolizin-2-one (5)

To a solution of 3,4-dihydro-β-carboline (3) (1.70 g, 10 mmol) in dry MeOH (40 ml), hydroxymethyleneacetylacetone (4) (1.40 g, 11 mmol) was added at 28°C with stirring under N_2 all at a time. After 10 min crystals started to

appear and the stirring was continued for 2 h more. The reaction mixture was filtered and the solid was recrystallised from MeOH-$CHCl_3$ to afford 5 (2.72 g, 98%), mp 318-320°C (lit.,[3] mp 316-317°C).

3-Acetyl-1,2,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine-2-ethylene thioketal (6)

A mixture of the compound **(5)** (2.80 g, 10 mmol), p-toluenesulfonic acid monohydrate (2.60 g, 14 mmol), and 1,2-ethanedithiol (3 ml, 36 mmol) in benzene (500 ml) was refluxed in a Dean-Stark apparatus and the reaction was monitored by tlc. After 3 h, the reaction mixture was allowed to cool and the benzene portion was decanted. It was washed with 2% $NaHCO_3$ solution followed by water, dried (Na_2SO_4) and concentrated. The gummy residue was taken in $CHCl_3$ (100 ml) containing little MeOH (2 ml). This was shaken with 2% $NaHCO_3$ solution, washed with water, dried (Na_2SO_4) and the solvent was evaporated. The solid formed from this and the decanted portion after removal of solvent benzene (3.34 g, 94%) was recrystallised from petroleum ether-$CHCl_3$ to afford **6** as colorless flakes, mp 218-220°C; ir ν_{max}(KBr): 3180, 1630, and 1615 cm^{-1}: uv (log ϵ): λ_{max}(MeOH) 221 (4.56) and 301 nm (4.44); ^{1}H-nmr ($CDCl_3$): δ 2.34 (s, 3H), 2.36-3.00 (m, 4H), 3.38-3.80 (m, 5H), 3.96 (m, 1H), 4.79 (dd, J=12, 5 Hz, 1H), 7.10-7.20 (m, 3H), 7.44 (s, 1H), 7.47-7.60 (m, 1H), and 8.19 (br s, 1H); ^{13}C-nmr (DMSO-d_6): δ 21.3(t), 26.6(q), 40.3(t), 40.8(t), 48.6(t), 49.8(t), 51.9(d), 61.3(s), 106.8(s), 107.6(s), 111(d), 117.6(d), 118.5(d), 121.1(d), 126.1(s), 131.9(s), 136.3 (s), 148.9(d), and 190.3(s); ms m/z (rel. int.): 356(M^+, 30), 355(28), 313 (66), 297(100), 295(91), 263(56), 169(37), 85(90), and 83(85); Anal. Calcd for $C_{19}H_{20}N_2OS_2$:C, 64.09; H, 5.66; N, 7.87. Found: C, 63.94; H, 5.61; N, 7.92.

(±)-E-Deplancheine (1)

To a solution of the thioketal **(6)** (356 mg, 1 mmol) in EtOH (25 ml), Raney Ni (W-2,2 g) was added, and the reaction mixture was stirred at 28°C for 1 h. The mixture was filtered over a celite bed and the filtrate was evapora-

ted to dryness in vacuo. The residue was crystallised from petroleum ether-$CHCl_3$ to yield the vinylogous amide **(7)** as colourless needles (253 mg, 96%), mp 147°C (lit.,[5] mp 146-147°C). A mixture of the amide **(7)** (266 mg, 1 mmol), $NaBH_4$ (400 mg, 10.5 mmol), and t-BuOH (15 ml) was refluxed with occasional addition of MeOH (3 ml) in portions for 3 h. When most of the starting material has been consumed (tlc), the reaction mixture was cooled, water (25 ml) was added and excess t-BuOH was removed in a rotavapor. The residue was extracted with $CHCl_3$ (3x30 ml), washed with water, dried (Na_2SO_4), and concentrated in vacuo to yield a gummy residue which was purified by column chromatography over silica gel. Eluates of petroleum ether-$CHCl_3$ (1:1) were mixed, solvent was evaporated and the residue was recrystallised from ether to yield (±)-E-deplancheine **(1)** (185 mg, 73%) as colorless needles, mp 159-161°C (lit.,[1b] mp 158°C).

Sodium cyanoborohydride reduction of the thioketal (6)

The thioketal **(6)** (356 mg, 1 mmol) was dissolved in glacial AcOH (20 ml), the solution was cooled to 10-15°C and $NaBH_3CN$ (315 mg, 5 mmol) was added under stirring in portions quickly. The reaction mixture was allowed to come to room temperature (28°C) and stirred for a further 30 min. Water (20 ml) was added to the reaction mixture and the excess acid was neutralised with 2% Na_2CO_3 solution. The neutralised mixture was extracted with $CHCl_3$ (3x30 ml), the organic layer was washed with water, dried (Na_2SO_4) and concentrated to afford a solid which was filtered using little MeOH. The solid was recrystallised from $CHCl_3$-MeOH to yield the alcohol **(8)** (250 mg, 69%), mp 252-254°C as colorless microfine needles; ir ν_{max}(KBr): 3510, 3200, 2850-2740 (Bohlmann bands), and 1090 cm^{-1}; uv (log ε): λ_{max} (MeOH) 224 (4.83) and 280 nm (4.23); ^{1}H-nmr (DMSO-d_6): δ 1.18 (d, J=6 Hz, 3H), 1.94 (m, 1H), 2.27 (br s, 1H), 2.54-3.24 (m, 4H), 3.36 (br s, 4H), 4.28 (m, 1H), 4.52 (d, J=5 Hz, 1H), 6.84-7.20 (m, 2H), 7.20-7.52 (m, 2H) and 10.77 (br s, 1H); ^{13}C-nmr (DMSO-d_6): δ 19.6(q), 21.4(t), 37.6(t), 38.4 (t), 49.2(t), 51.9(t), 52.2(t), 55.1(t), 58.6(d), 65.1(d), 70.1(s), 106.7 (s), 110.0(d), 117.0(d), 118.0(d), 120.1(d), 126.5(d), 134.5(d), and 135.5

(d); ms m/z (rel. int.): 360(M^+, 18), 315(11), 299(15), 267(41), 255(26), 184(100), 170(25), 168(31), 156(26), and 45(32); Anal. Calcd for $C_{19}H_{24}N_2OS_2$: C, 63.39; H, 6.72; N, 7.78. Found: C, 63.30, H, 6.76; N, 7.83. The mother liquor of **8** was evaporated and the residue was chromatographed on silica gel. The eluates from petroleum ether-$CHCl_3$ (1:1) yielded the ketone **(9)** (43 mg, 12%) as colorless fine needles, mp 240-242°C; ir ν_{max} (KBr): 3350, 2850-2760 (Bohlmann bands), and 1690 cm^{-1}; uv (log ϵ): λ_{max} (MeOH) 271 (3.68), 280 (3.69), and 289 nm (3.62); ^{1}H-nmr (DMSO-d_6): δ 2.02 (m, 1H), 2.34 (s, 3H), 2.40-3.32 (m, 9H), 3.30 (s, 4H), 6.90-7.16 (m, 2H), 7.20-7.54 (m, 2H) and 10.80 (br s, 1H); Anal. Calcd for $C_{19}H_{22}N_2OS_2$: C, 63.74; H, 6.19; N, 7.83. Found: C, 63.65; H, 6.23; N, 7.78.

The $CHCl_3$ eluates gave a further 45 mg to yield a total of 82% of the alcohol **(8)**.

Dehydration of the alcohol (8)

To a suspension of the alcohol **(8)** (360 mg, 1 mmol) in pyridine (1 ml), $POCl_3$ (0.3 ml, 3.2 mmol) was added and the resulting homogeneous reaction mixture was heated for 30 min at 80-90°C. The solid mass formed was decomposed with crushed ice, neutralised with 20% NH_4OH solution and extracted with $CHCl_3$ (3x25 ml). The $CHCl_3$ layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to remove traces of pyridine completely. The residue was recrystallised from MeOH to yield the olefin **(10)** (313 mg, 92%), mp 114-116°C; ir ν_{max}(KBr): 3300-3130 and 2850-2720 (Bohlmann bands) cm^{-1}; uv (log ϵ): λ_{max}(MeOH) 221 (4.81) and 272 nm (4.00); ^{1}H-nmr (DMSO-d_6): δ 1.53 (d, J=7 Hz, 3H), 2.38 (m, 1H), 2.76-3.26 (m, 6H), 3.32 (s, 4H), 3.42 (m, 1H), 4.80 (m, 1H), 6.88-7.20 (m, 2H), 7.20-7.56 (m, 2H), and 10.76 (br s, 1H); ms m/z (rel. int.): 342 (M^+, 23), 341(79), 340 (21), 281(71), 249(52), 221(11), 184(55), and 169(100); Anal. Calcd for $C_{19}H_{22}N_2S_2$: C, 66.72; H, 6.48; N, 8.19. Found: C, 66.63; H, 6.52; N, 8.17.

Flavopereirine (2)

To a solution of the olefin **(10)** (171 mg, 0.5 mmol) in ethanol (15 ml),

Raney Ni (W-2, 1.2 g) was added in portions and the reaction mixture was stirred with tlc monitoring [silica gel, petroleum ether-EtOAC (3:2)]. After the disappearance of the starting material (1 h), the reaction mixture was filtered over a bed of celite, washed with EtOH and the filtrate was evaporated under reduced pressure to afford **11** as a glassy film (94 mg, 74%), ^{1}H-nmr ($CDCl_3$): δ 1.06 (t, J=7 Hz, 3H), 2.02 (q, J=7 Hz, 1H), 2.12-3.90 (m, 7H), 5.54 (m, 1H), 7.04-7.70 (m, 4H), and 7.84 (br s, 1H); ms m/z (rel. int.): 252 (M^+, 68), 237(5), 223(16), 169(100), and 167(65).

To a solution of **11** (126 mg, 0.5 mmol) in AcOH (15 ml), DDQ (456 mg, 2 mmol) and 70% $HClO_4$ (0.02 ml) were added and the reaction mixture was heated for 4 h at 80-90°C. Solid formed was filtered and recrystallised (MeOH) to afford flavopereirine perchlorate (**2**) (140 mg, 82%), mp 316-317°C (dec.) [lit.,[7] mp 316-317°C (decomp.)].

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