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Synthetic Studies in Indolo[2,3-a]quinolizidine System

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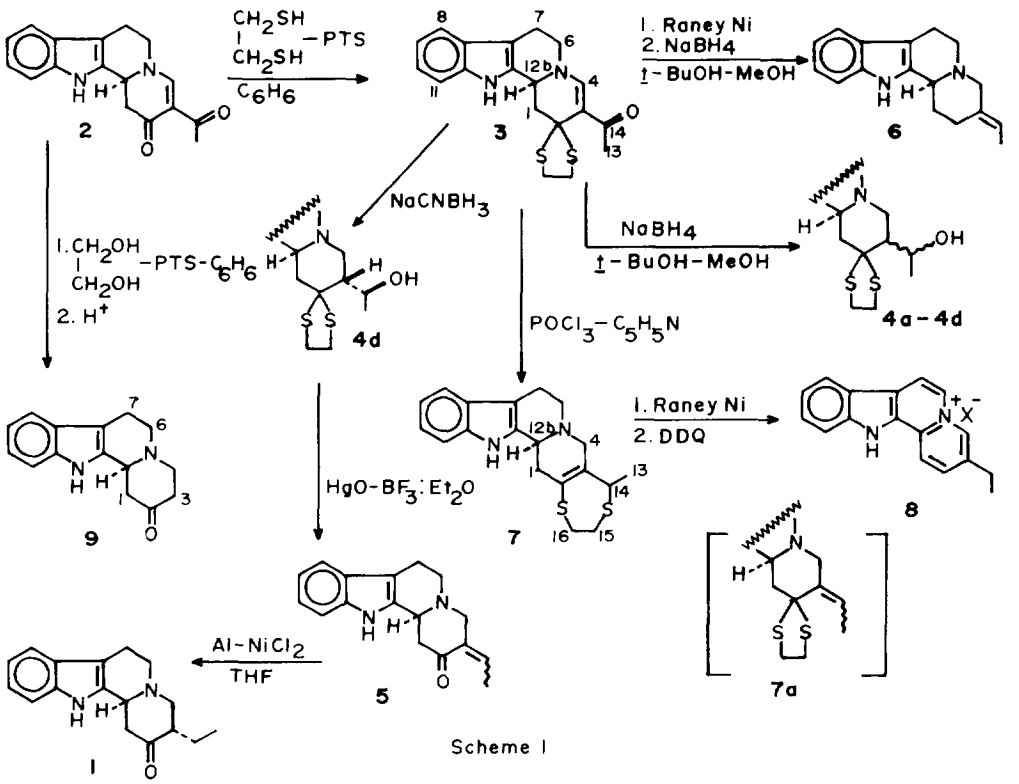
Abstract: Synthesis of *trans*-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-one (**1**) and assignment of stereo chemistry of the diastereoisomeric alcohols, 3-(α-hydroxyethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-ethylene thioketals (**4a-4d**) has been discussed.

Indolo[2,3-a]quinolizidine ring system has continued to receive the attention of synthetic organic chemists because of its presence in a large number of indole alkaloids[1]. In particular indolo[2,3-a]quinolizidin-2-one including its 3-ethyl derivatives are known intermediates in the synthesis of important alkaloids[2]. In our effort to obtain a common intermediate for alkaloids of such system the key intermediate 3-acetyl-1,2,6,7,12,12b-hexahydroindolo[2,3-a]quinolizin-2-one (**2**) was synthesised. Regiospecific thioketalisation of **2** followed by desulphurisation and standard reductive or oxidative procedures afforded[3] the alkaloids, (±)-E-deplancheine (**6**) and flavopereirine (**8**) respectively. On the other hand ketalisation of **2** followed by acid hydrolysis gave in near quantitative yield the yohimbine alkaloid precursor, indolo[2,3-a]quinolizidin-2-one (**9**)[4].

Earlier we have reported[3] that reduction of the thioketal **3** with $NaCNBH_3$ in HOAc yielded only one diastereoisomeric alcohol **4d**. This is possibly due to prior reduction of the intermediate iminium followed by stereoselective protonation from β-face assisted by lone pair of N-5 and preferential attack of the hydride on the unconjugated carbonyl by the rule of steric control of asymmetric induction. The formation of all the four diast-



Scheme I

ereoisomeric alcohols (**4a - 4d**) when **3** was treated with $NaBH_4$-*t*-BuOH-MeOH could possibly be due to prior 1,2-reduction of the iminium double bond followed by isomerisation of the resulting unconjugated carbonyl intermediate in the alkaline medium before further reduction. The alcohols have been separated on a silica gel column and characterised from their physical data.

The *trans*-ring fusion in all the four alcohols (**4a - 4d**) was indicated by the presence of Bohlmann bands between 2850-2740 cm^{-1} in their IR spectra. The upfield chemical shift of the γ-carbon at C-1 by 6 ppm in both **4a** and **4b** compared to that of **4c** and **4d** indicates that the -CHOHMe side chain is β-axial in both **4a** and **4b** whereas it is α-equatorial in **4c** and **4d**. This is also further corroborated by *NOE* experiments. Irradiation of the proton at C-3 in both **4a** and **4b** causes signal enhancement of the α-protons at C-1

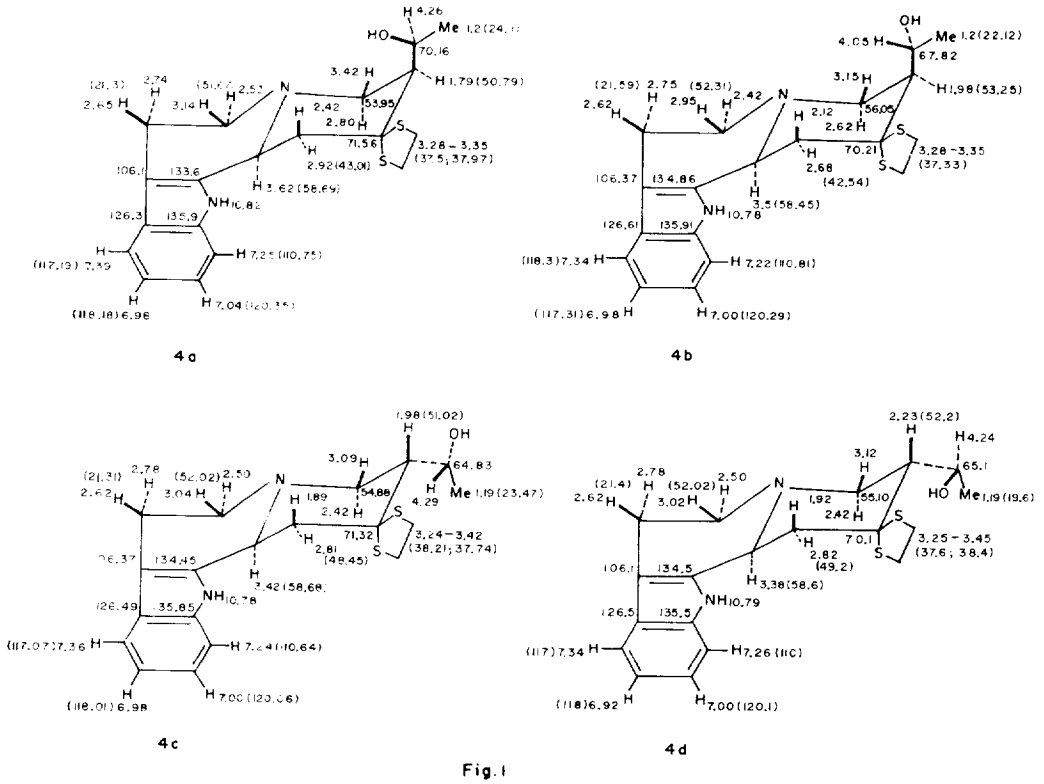


Fig.1

and C-4 respectively. *NOE* of β-protons at δ 2.42 (C-1) and δ 3.42 (C-4) resulting from irradiation of the -OH proton in **4a** shows that -OH group is close to both the protons. Further, the proton α to the hydroxy group (-*C*HOHMe) appears at a lower field (δ 4.26) in **4a** compared to that in **4b** (δ 4.05). Alsó irradiation of the proton at δ 4.05 in **4b** causes *NOE* at δ 2.12 (β-H at C-1) and *vice-versa*. Thus in **4a**, the chiral centre of -CHOHMe group has S and in **4b** R configuration respectively. The proton at C-3 in **4c** appears at δ 1.98 and in **4d** at δ 2.23. Scrutiny of similar systems[5] revealed that in cases where the chiral centre of -CHOHMe group has R configuration, the C-3 proton appears at a higher field compared to that with S. Thus, the major product **4d** (also the major product during $NaCNBH_3$ reduction of **3**) has S configuration for the chiral centre of -CHOHMe group. In all the four alcohols (**4a - 4d**; Fig.1) chemical shifts have been assigned on the basis of *2D* correlation experiments including *TOCSY*, *HMBC* and *HMQC*.

Dehydration of the alcohol **4d** using $POCl_3$-pyridine afforded an olefin, the structure of which was originally assigned[3] as **7a**. Failure of **7a** to undergo usual Hg salt assisted hydrolytic cleavage necessitated proper analysis of its PMR spectrum. The rather high field signals for both the Me group doublet at δ 1.53 (δ 1.56 in $CDCl_3$) and one proton quartet at δ 4.08 (δ 4.26 in $CDCl_3$) in DMSO-d_6 required a rearrangement of the olefinic bond. This was further confirmed by the CMR spectrum which showed signals at δ 145.04 (s), 123.06 (s) and 40.14 (d) for the carbons at C-2, C-3 and C-14 respectively. Moreover, the absence of any signal for a typical thioketalised carbon and a trisubstituted olefin establishes structure **7** for the compound.

On the other hand dethioketalisation of the alcohol **4d** using Hgo-BF_3:Et_2O afforded the enone **5** as the only product. Reduction of **5** using Al-$NiCl_2$ mixture[6] afforded the desired ketone **1** in good yield, the physical data of which are in agreement with the one prepared by us following O'Rell *et al*[2].

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a JASCO 700 spectrophotometer. ^1H NMR spectra were measured on a JEOL FX - 100FT spectrometer using TMS as internal standard. All the high field NMR spectra were recorded on a Varian XL GEMA 300 spectrometer equipped with a GEMINI 300 BB computer. Mass spectra were run on a JEOL AX-500 spectrometer at 70 eV. Petroleum ether refers to the fraction boiling in the range 60-80°C.

Sodium borohydride reduction of thioketal 3 to alcohols 4a - 4d

A mixture of the thioketal (356 mg, 1 mmol), $NaBH_4$ (456 mg, 12 mmol), and *t*-BuOH (20 ml) was refluxed with occasional addition of MeOH (5 ml) in portions for 4h. Cold water (25 ml) was added to the reaction mixture and the excess *t*-BuOH was removed in a rotavapor. The residue was extracted with $CHCl_3$ (3x30 ml), dried (Na_2SO_4), concentrated and then chromatographed over silica gel. Petroleum ether-$CHCl_3$ (1:1) eluates gave a solid which was recrystallised from petroleum ether-$CHCl_3$ to furnish **4a** as colourless flakes (90

mg, 25%): mp 255-256°C; IR : ν 3500, 3280, 2850-2750, 750 cm^{-1}; MS (m/z, %): 360 (M^+,27), 184(100), 169(25). Anal.Calcd for $C_{19}H_{24}N_2OS_2$: C, 63.39; H, 6.72; N, 7.78. Found C, 63.26; H, 6.64; N, 7.69. Solid obtained from elu-ates of petroleum ether-$CHCl_3$ (1:3) on recrystallisation from petroleum ether-$CHCl_3$ afforded **4b** (45 mg; 12.5%) as colourless hard crystals: mp 240-242°C; IR : ν 3500, 3280, 2860-2745, 750 cm^{-1} ; MS (m/z, %): 360(M^+,32), 315 (10), 299(17), 184(100), 169(30). Anal.Calcd for $C_{19}H_{24}N_2OS_2$: C, 63.39; H, 6.72; N, 7.78. Found C, 63.28; H, 6.80; N, 7.90. The solid from eluates of $CHCl_3$ was recrystallised from petroleum ether-$CHCl_3$ to yield **4c** (45mg; 12.5%) as hard crystals: mp 237-239°C; IR : ν 3456, 3210, 2850-2726 cm^{-1} : MS (m/z, %), 360(M^+,18), 315(8), 299(10), 197(11), 184(100), 169(22). Anal. Calcd for $C_{19}H_{24}N_2OS_2$: C,63.39; H, 6.72; N, 7.78. Found C, 63.24; H, 6.81; N, 7.69. Further elution with $CHCl_3$:MeOH (98:2) afforded **4d** which was recr-ystallised from $CHCl_3$:MeOH as colourless needles (135 mg; 37.5%): mp 252 -254°C; IR : ν 3510, 3200, 2850-2740 cm^{-1}; MS (m/z, %): 360(M^+,18), 315(11), 299(15), 184(100), 170(25), 156(26). 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, 7.80.

3-Ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-one (5)

To a stirred solution of 428 mg (1.25 mmol) of the thioketal **4d** in a THF-Water mixture (9.5 : 0.5 ml), 542 mg (2.5 mmol) of red HgO and 0.48 ml of BF_3:Et_2O were added. After 14 h stirring the solvent was decanted and the remainings carefully washed with little THF. The residue after removal of solvent was extracted with CH_2Cl_2 (3x25 ml). This extract was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), concentrated and the residue was chromatographed over silica gel. The $CHCl_3$-MeOH eluates (99 : 1) afforded a solid which was recrystallised from petroleum ether-$CHCl_3$ to afford **5** (246 mg; 74%) as colurless fine needles: mp 154-156°C; IR : ν 3318, 2850-2752, 1683, 1611, 737 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.80 (d,J=7Hz,3H,*Me*), 2.24-3.44 (m,7H), 3.80 (dd,J=12Hz,1H,*H-12b*), 4.04 (d,J=15Hz,1H), 6.96 (q,J=7Hz,1H,*H-14*), 7.08-7.58 (m,4H,*Ar-H*), 8.08 (brs,1H,*NH*); ^{13}C NMR ($CDCl_3$) : δ 13.47 (q, *C-13*), 21.43 (t,*C-7*), 44.18 (t,*C-1*), 52.02 (t,*C-6*), 54.95 (t,*C-4*), 55.59 (d, *C-12b*), 108.01 (s,*C-7a*), 111.05 (d,*C-11*), 118.01 (d,*C-8*), 119.24 (d,*C-9*),

121.52 (d,*C-10*), 126.70 (s,*C-7b*), 133.28 (s,*C-3*), 133.98 (s,*C-12a*), 135.97 (d,*C-14*), 136.44 (s,*C-11a*), 196.58 (s,*C-2*); MS (m/z, %): 266 (M^+,100), 265 (70), 251(10), 237(16), 223(25), 169(85). Anal.Calcd for $C_{17}H_{18}N_2O$: C, 76. 66; H, 6.81; N, 10.52. Found C, 76.59; H, 6.90; N, 10.43.

***trans*-3-Ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-one (1)**

To a freshly mixed Al powder (540 mg, 20 mmol) and $NiCl_2.6H_2O$ (7.14 g; 25 mmol), was added a solution of **5** (160 mg; 0.6 mmol) in freshly distilled THF (25 ml). A vigorous exothermic reaction occurs after a few minutes and it subsides on its own. After disappearance of the starting material (TLC), the reaction mixture was diluted with THF (50 ml) and filtered. Filtrate concentrated and the residue purified over basic alumina coloumn. Eluates of petroleum ether-$CHCl_3$ (1:3) were combined, concentrated and the solid recrystallised from petroleum ether-$CHCl_3$ to afford the ketone **1** as colourless flakes (120 mg ; 75%): mp 205-207°C (lit[2] mp 208-209°C).

Dehydration of alcohol 4d

The dehydration of **4d** was done as reported earlier[3] to obtain the olefin **7** : mp 114-116°C ; ^{13}C NMR ($CDCl_3$) : δ 17.91 (q,*C-13*), 21.19 (t,*C-7*), 31.24,31.95 (2xt,*C-15/C-16*), 39.73 (t,*C-1*), 40.14 (d,*C-14*), 51.43 (t,*C-6*), 55.53 (d,*C-12b*), 55.93 (t,*C-4*), 108.11 (s,*C-7a*), 110.70 (d,*C-11*), 118.01 (d,*C-8*), 119.24 (d,*C-9*), 121.34 (d,*C-10*), 123.06 (s,*C-3*), 126.90 (s,*C-7b*), 133.63 (s,*C-12a*), 136.36 (s,*C-11a*), 145.04 (s,*C-2*).

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