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SYNTHESIS OF INDOLO[2,3-a]QUINOLIZIDINE-3-ONE

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Abstract : The title compound **1** has been synthesised through the intermediacy of the salt **5** obtained by acid hydrolysis of the optically active β-carboline derivative 10,11-cyclohexylidene-12β-hydroxy-13β-(1-tetrahydro-β-carbolinyl)tetrahydrofuran (**4**).

The synthesis of β-carboline derivatives have continued to evoke interest particularly because of the important physiological properties exhibited by a number of them. Earlier we have reported the synthesis of indolo[2,3-a]-quinolizidin-2-one, an intermediate for Yohimbine and related alkaloids.[1] In an effort to obtain a common intermediate for aspidosperma type alkaloids, tryptamine (**2**) was condensed with the anhydrosugar, di-(1,2-O-cyclohexylidene-α-D-xylo-pentodialdofuranose-5-hydrate)-5,5':3',5-dianhydride (**3**) obtained from α-D-glucose[2] (scheme 1). This afforded an optically active β-carboline derivative, 10,11-O-cyclohexylidene-12β-hydroxy-13β-(1-tetrahydro-β-carbolinyl)tetrahydrofuran (**4**) in

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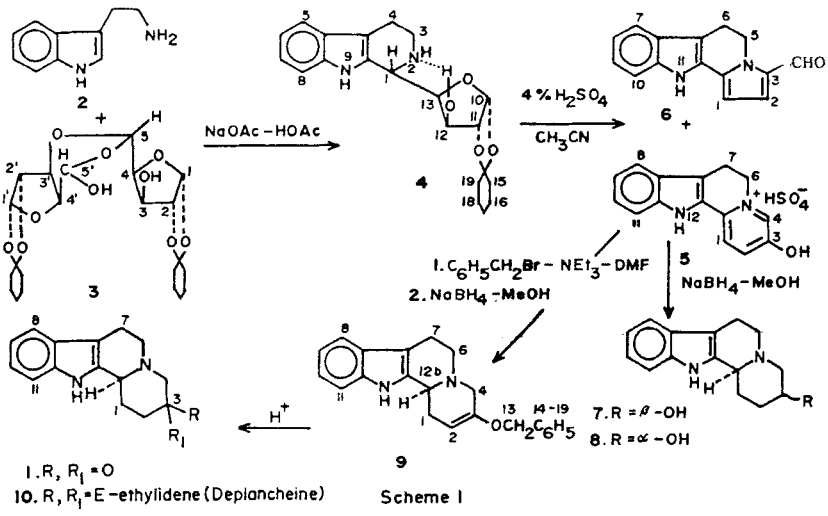
58% yield, mp 200-201°C; $[\alpha]_D^{25}$=-54° (c=0.48, $CHCl_3$). The structure of this new potential intermediate **4** was assigned mostly from NMR spectral analysis and Dreiding model wherein the H-1 hydrogen is β and the lone pair of nitrogen (N-2) could intramolecularly hydrogen bond to the hydroxy group of the tetrahydrofuran ring.

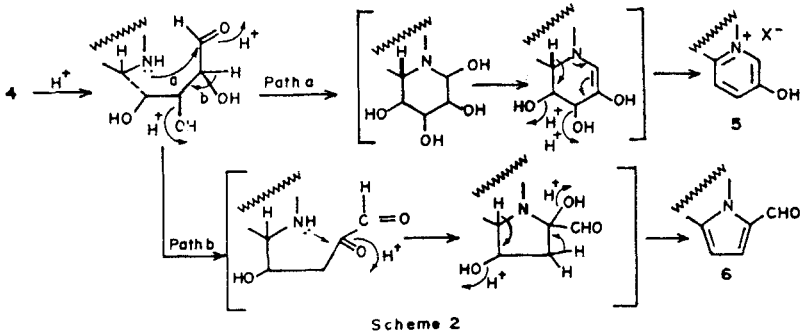
Acid hydrolysis of **4** with 4% sulphuric acid in acetonitrile gave the quaternary salt, 3-hydroxy-6,7-dihydro indolo[2,3-a]quinolizinium hydrogen sulphate (**5**) along with an interesting minor product **6** characterised as 3-formyl-5,6-dihydroindolo[2,3-a]indolizine. The ^1H NMR spectrum of **6** exhibited the characteristic aldehyde proton as a singlet at δ 9.58, two doublets at δ 6.38 and 7.02 with J=6Hz for the two protons at H-1 and H-2 apart from signals for aromatic, the two methylene protons of the β-carboline and the indole nitrogen.

The formation of **5** could be rationalised on the basis of a plausible straight forward cyclisation after hydrolysis by condensation of the amine and the aldehyde (path a) followed by dehydrations whereas formation of **6** requires a dehydration (path b) immediately following the opening of cyclohexylidene ring resulting in a dicarbonyl intermediate which undergoes cyclisation with concomitant dehydration (scheme 2).

As anticipated sodium borohydride reduction of **5** in methanol at room temperature yielded in 90% a 3:7 mixture of



Scheme 1



Scheme 2

the two epimeric alcohols **7**, mp 160-161°C and **8**, mp 200-201°C, the physical data of which are in agreement with those reported.[3] Benzylation of the salt **5** using benzyl bromide in a solution of DMF and triethylamine followed by $NaBH_4$ reduction afforded the known[4] enol ether **9**. Hydrolysis of the enol ether **9** with 6N HCl : MeOH (1:1) under reflux for 1 h afforded

the ketone **1** a precursor[3,4] for the alkaloid deplancheine (**10**) in near quantitative yield.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a JASCO-700 spectrophotometer. UV spectra in MeOH were taken on a Hitachi U-2000 spectrophotometer. ^1H NMR spectra were measured on a JEOL FX-100 FT spectrometer using TMS as internal standard and the mass spectra were recorded on a JEOL AX-500 spectrometer at 70 eV. Petroleum ether refers to the fraction boiling in the range 60-80°C. Compound **3** was prepared following the reported[2] procedure. The known[3] alcohols **7** and **8** were obtained by routine $NaBH_4$ reduction of the salt **5** in MeOH followed by column chromatography over basic alumina.

10,11-O-cyclohexylidene-12 β-hydroxy-13 β-(1-tetrahydro-β-carbolinyl)tetrahydrofuran (4)

A mixture of 1.6g (10 mmol) of tryptamine (**2**) and 2.5g (5.4 mmol) of the dimeric sugar **3** in a 1:1 aqueous methanolic solution (50 ml) of 1N NaOAc and 1N HOAc was heated under stirring at 60°C. After most of the starting material has been consumed (monitored by tlc, 5h) the reaction mixture was evaporated under reduced pressure to remove the methanol. It was then neutralised with $NaHCO_3$ solution and extracted with

chloroform. The extract was dried (Na_2SO_4), solvent evaporated and the residue chromatographed over basic alumina. Petroleum ethr-chloroform (1:1) eluates were combined and concentrated to afford **4** (2.15g; 58%) which was recrystallised from petroleum ether-chloroform : mp 200-201°C; $[\alpha]_D^{25}$=-54.0°C (c=0.48, $CHCl_3$); IR : ν 3454, 3088, 1034, 735 cm^{-1}; UV : λ_{max} 222.5 (log ϵ 4.06), 278.5 (3.41); ^1H NMR ($CDCl_3$) : δ 1.4-1.9 (brs, 10H), 2.64-2.84 (m,2H,H-4), 2.9-3.20 (m,2H,H-3), 3.3-3.6 (m,2H,OH, NH), 4.24 (m,1H,H-11), 4.4-4.60 (m,3H,H-1,H-12,H-13), 6.04 (d,J=5Hz,1H,H-10), 7.04-7.60 (m,4H,Ar-H), 8.44 (brs,1H,NH); ^{13}C NMR ($CDCl_3$) : δ 21.89 (t,C-4), 23.47 (t,C-18), 23.76 (t,C-16), 24.75 (t,C-17), 35.23 (t,C-19), 36.22 (t,C-15), 42.71 (t,C-3), 52.78 (d,C-1), 75.42 (d,C-12), 81.33 (d,C-13), 85.07 (d,C-11), 104.78 (d,C-10), 109.35 (s,C-14), 110.93 (d,C-8), 112.45 (s,C-4a), 118.01 (d,C-5), 119.18 (d,C-6), 121.63 (d,C-7), 126.90 (s,C-4b), 131.17 (s,C-9a), 136.08 (s,C-8a); MS m/z (rel. int.): 370(M^+,90), 327(25), 271(20), 255(28), 237(22), 213(50), 199(30), 184(84), 172(98), 171(100); Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found : C, 67.97; H, 7.14; N, 7.63.

3-Hydroxy-6,7-dihydroindolo[2,3-a]quinolizinium hydrogen sulphate (5)

Compound **4** (370 mg, 1 mmol) was stirred in a solution of 0.3 ml conc. H_2SO_4, 1 ml water and 9 ml CH_3CN at room temperature for 72 h. The solid formed was filtered and recrystallised from aqueous methanol to afford **5** (140 mg; 42%)

as greenish yellow needles : mp 296-298°C (dec.); IR : ν 3376, 3172, 1590, 1565, 1529, 742 cm^{-1}; UV : λ_{max} 224 (log ϵ 4.17), 263(3.67), 322(4.19), 413(3.91); ^1H NMR (DMSO-d_6) : δ 3.32 (t,J=8Hz,2H,H-7), 4.84 (t,J=8Hz,2H,H-6), 7.04-7.76 (m,4H,Ar-H), 7.88 (d,J=8Hz,1H,H-2), 8.06 (d,J=8Hz,1H,H-1), 8.44 (brs,1H,H-4), 12.18 (brs,1H,NH); MS m/z (rel. int.) : 236(M^+,45), 208(18), 194(20), 185(25), 184(27), 169(25), 138(78), 111(100); Anal. Calcd. for free base $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found : C, 76.16; H, 5.05; N, 11.94.

3-Formyl-5,6-dihydroindolo[2,3-a]indolizine (6)

The filtrate from the above reaction mixture was diluted with water (15 ml) and neutralised with $NaHCO_3$ and extracted into chloroform (3x20 ml). The extract was dried (Na_2SO_4), concentrated and the residue chromatographed over basic alumina. Eluates from petroleum ether-chloroform mixture (75:25) afforded a solid (17 mg, 8%) which was recrystallised from petroleum ether-chloroform to the amino aldehyde **6** : mp 162-163°C; IR : ν 3168, 1632, 771, 733 cm^{-1}; UV : λ_{max} 216.5 (log ϵ 4.23), 267.5 (3.98), 298.5 (3.69), 382 (4.34); ^1H NMR ($CDCl_3$) : δ 3.4 (t,J=8Hz,2H,H-6), 4.8 (t,J=8Hz,2H,H-5), 6.38 (d,J=6Hz,1H,H-1), 7.02 (d,J=6Hz,1H,H-2), 7.08-7.68 (m,4H,Ar-H), 8.34 (brs,1H,NH), 9.58 (s,-CHO); MS m/z (rel. int.) : 236(M^+, 100), 235(96), 207(30), 206(32); Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12, N, 11.86. Found : C, 76.14; H, 5.21; N, 11.94.

3-Benzyloxy-1,4,6,7,12-12b-hexahydroindolo[2,3-a]quinolizine (9)

To a solution of compound **5** (334 mg, 1 mmol) in DMF (1 ml) and triethylamine (2 ml), benzyl bromide (342 mg, 2 mmol) was added under stirring at room temperature for 8 h. The solvents were removed under reduced pressure and the residue dissolved in methanol (15 ml). $NaBH_4$ (390 mg, 10 mmol) was added in portions under stirring to the methanolic solution at 10°C and the reaction mixture was stirred for a further 2 h. Water (20 ml) was added to decompose the excess hydride and the mixture was extracted with chloroform. The extract was dried (Na_2SO_4), concentrated and the residue was chromatographed over basic alumina to afford the ether **9** (220 mg, 70%) as colourless hard needles : mp 200-201°C; IR : ν 3400, 2850-2740 (Bohlmann bands), 1674, 739 cm^{-1}; UV: λ_{max} 223 (log ϵ 4.42), 279.5 (3.71): ^1H NMR (DMSO-d_6) : δ 2.04 (m,1H), 2.50-3.04 (m,4H), 3.08-3.58 (m,4H), 4.84 (s,2H), 4.96 (d,J=6Hz,1H), 6.84-7.16 (m,2H), 7.20-7.34 (m,2H), 7.40 (s,5H), 10.8 (brs,1H,NH); ^{13}C NMR (DMSO-d_6) : δ 21.1 (t,C-7), 28.8 (t,C-1), 51.38 (t,C-6), 55.12 (t,C-4), 55.80 (d,C-12b), 68.11 (t,C-13), 91.90 (t,C-2), 106.31 (s,C-3), 110.80 (d,C-11), 117.40 (d,C-8), 118.18 (d,C-9), 120.29 (d,C-10), 126.49 (s,C-7b), 127.37 (2xd, C-16,C-18), 127.48 (d,C-17), 128.13 (2xd,C-15,C-19), 135.21 (s,C-14), 136.1 (s,C-12a), 137.38 (s,C-11a), 151.18 (s,C-3); MS m/z (rel. Int.) : 330(M^+,35), 241(100), 240 (98), 209(16), 184(40), 169(74), 91(70); Anal. Calcd. for

$C_{22}H_{22}N_2O$: C, 80.07; H, 6.72; N, 8.49. Found : C, 79.98; H, 6.78; N, 8.57.

Indolo[2,3-a]quinolizidin-3-one (1)

A solution of **9** (330 mg, 1 mmol) in a 1:1 mixture (20 ml) of 6N HCl and methanol was refluxed for 1 h. The reaction mixture was cooled, diluted with water (20 ml), neutralised with $NaHCO_3$ and extracted into chloroform (3x25 ml). The organic layers were combined, dried (Na_2SO_4) and solvent was removed under reduced pressure to yield a gummy solid which was recrystallised from petroleum ether-chloroform to indolo[2,3-a]quinolizidin-3-one (1; 218 mg, 91%) as pale yellow needles; mp 118-119°C (Previous workers have not crystallised the compound but the physical data reported[3,4] are in agreement with ours).

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