SYNTHESIS OF (±)-DEPLANCHEINE

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Abstract - The indole alkaloid (±)-deplancheine (1) has been synthesized utilizing the intermediate 3-acetyl-1,2,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (6) prepared in two synthetic steps from readily available starting materials.

(±)-Deplancheine (1), an indole alkaloid having E-configuration of ethylidene side chain at C-3 was first synthesized by Winterfeldt and his co-workers[1] even before the isolation of the (+)-base from a natural source, viz. Alstonia deplanchei (Apocynaceae) by Besselièvre et al.[2] who also synthesized the racemic base. Several other syntheses have since been reported[3-5], but all of them involved multisteps and difficultly preparable starting materials. Herein we report some simple and modified syntheses of the title compound through the key intermediate 3-acetyl-1,2,6,7,12,12b-hexahydroindolo[2,3-a] quinolizine (6).

Condensation of 3-acetylindole (2)[6] and 3-(1,1-ethylenedioxyethyl)pyridine (3)[7] in presence of iodine at water-bath temperature afforded the quaternary iodide salt (4), mp 117-118°C (H_2O), in 65% yield. Reduction of 4 with $LiAlH_4$ in THF led to the uncyclised product 5 (61%). Reductive cyclisation could, nevertheless, be brought about with $(^tBuO)_3$ LiAlH followed by $LiAlH_4$ reduction to obtain the desired vinylogous tertiary amide (6)[8] in 44% yield. Further reduction with $LiAlH_4$ in THF under reflux afforded only 0.5% of 1 and its Z-isomer, contrary to the recent claim[3] of 20% yield. The major products (Scheme 1) of the reaction in our hands were identified as 7 (40%) and 8 (26%) besides 9 (4%).

The trans ring fusion in the quinolizines (7)-(9) was indicated by the characteristic Bohlmann bands. That the hydroxyethyl side chain is axial in 7 and equatorial in 8 became evident from the upfield shift of the signals for C-1(γ), C-2(β), C-3(α) and C-4(β) carbons by 5.7, 0.2, 1.9 and 1.7 ppm in the ^{13}C nmr spectrum of 7 compared to those of 8. The above contention was also supported by acetylation of 7 and 8. Thus, whereas 8 easily underwent acetylation with Ac_2O/Py at room temperature, 7 had to be heated at 100°C to give O-acetylated products 10 and 11 respectively. Presumably, the hydroxy group in 7 is hydrogen-bonded with the lone pair of nitrogen (Fig.A) while it must be free in 8 (Fig.B). It may be pointed out that the spectrum of 8, however, displayed pairs of signals for C-2, C-3, C-4, C-1' and C-2' indicating it to be a mixture of two diastereoisomers.

The equatorial orientation of the acetyl group in 9 was derived from the fact that it furnished 8 on reduction with $NaBH_4$.

Several approaches (Scheme 1) were made to improve upon the yield of the desired (+)-deplancheine (1) from the vinylogous amide (6) and the results are given as follows : (i) Reduction with $LiAlH_4$-$AlCl_3$ (1:1) in diethyl ether under reflux afforded 1 in 18% yield together with its Z-isomer and 9 in traces; (ii) Thermal decomposition of the p-tosyl hydrazone derivative (13) of 9 (obtained in 14% yield from 6 by $LiAlH_4$ reduction at room temperature with sodium methoxide[9] in dry diglyme produced 1 in 65% yield along with a minor amount (~5%) of Z-isomer. The best results so far have, however, been obtained by (iii) the reaction with triethyloxonium tetrafluoroborate in CH_2Cl_2 at room temperature and subsequent reduction of the resulting imino ether with $NaBH_4$ to furnish 1 in 23% yield with 15% of the enol ether (12).

EXPERIMENTAL

Mps, taken in open capillaries, are uncorrected. Ir spectra were recorded in KBr pellets on a Perkin-Elmer 177 Infrared spectrophotometer; ^1H and ^{13}C nmr spectra were measured on a JEOL FX-100 FT nmr spectrometer using TMS as internal standard and DMSO-d_6 as the solvent unless otherwise stated and the mass spectra (EI) were taken on a Hitachi RMU-6L instrument.

3-Acetylindole (2)

It was prepared according to the procedure of Saxton[6]. ^1H nmr : δ 2.42 (s,3H), 7.20 (m,2H), 7.50 (m,1H), 8.20 (m,1H), 8.22 (s,1H) and 11.76 (s,1H).

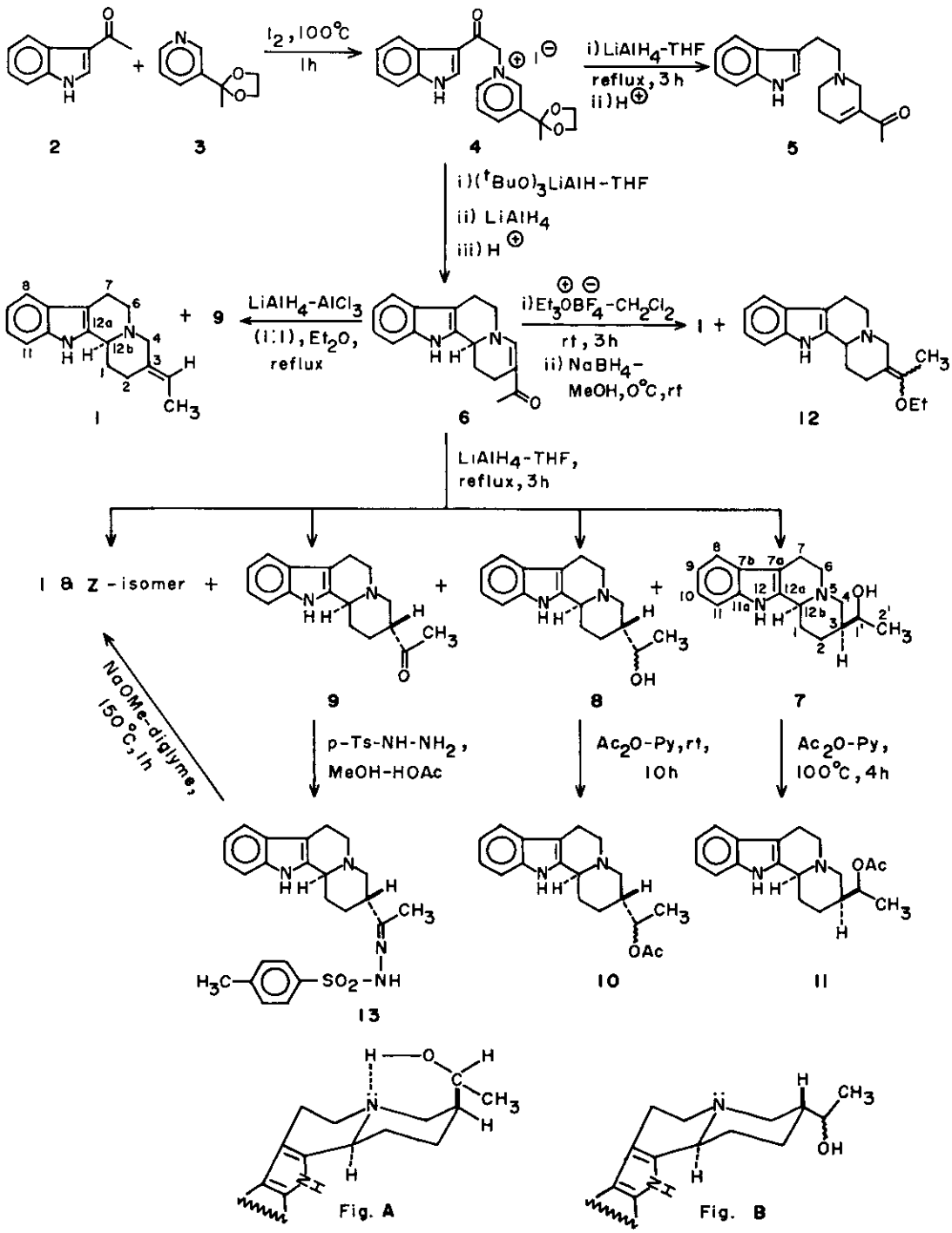
3-(1,1-Ethylenedioxyethyl)pyridine (3)

Compound 3 was synthesized following the procedure of Anderson, Jr. and Berkelhammer[7]. ^1H nmr ($CDCl_3$): δ1.66 (s,3H), 3.68-4.22 (m,4H), 7.30 (dd,1H, J=8 and 5 Hz), 7.80 (td,1H, J=8 and 2 Hz), 8.56 (dd,1H, J=5 and 2 Hz) and 8.80 (d,1H, J=2 Hz).

1-[2-(3-Indolyl)-2-oxoethyl]-3-[1,1-ethylenedioxyethyl]pyridinium Iodide (4)

Compound 2 (954 mg, 6 mmol) was suspended in the ethylene ketal 3 (2.97 g, 18 mmol) and heated on a water - bath till most of the acetylindole dissolved. Iodine (1.52 g, 6 mmol) was added and heating continued for 1 h with occasional shaking. The molten mass was cooled, the thick residue was extracted with hot water (4x10 ml) and filtered through cotton. The filtrate was kept at room temperature and the oily product crystallised on scratching. The yellow solid material was filtered, dried and recrystallised from hot water to furnish 1.78 g of 4; ir ν_{max} : 3390, 1660, 1645 and 1585 cm^{-1}; ^1H nmr : δ 1.70 (s,3H), 3.68-4.32 (m,4H), 6.32 (s,2H), 7.26 (br m,2H), 7.60 (br m,1H), 8.10 (br m,1H), 8.30 (br d,1H, J=8 Hz), 8.58 (d,1H, J=2 Hz), 8.73 (br d,1H, J=8 Hz), 8.58 (d,1H, J=2 Hz), 8.73 (br d,1H, J=8 Hz), 9.03 (br d,1H, J=6 Hz), 9.12 (br s,1H) and 12.24 (s,1H).

Scheme I


I2, 100°C
1h
i) LiAlH4-THF
reflux, 3h
ii) H⊕
2
3
4
5
i) (tBuO)3LiAlH-THF
ii) LiAlH4
iii) H⊕
LiAlH4-AlCl3
(1:1), Et2O,
reflux
i) Et3OBF4-CH2Cl2
rt, 3h
ii) NaBH4-
MeOH, 0°C, rt
1
9
6
12
LiAlH4-THF,
reflux, 3h
1 & Z-isomer +
9
8
7
NaOMe-diglyme,
150°C, 1h
p-Ts-NH-NH2,
MeOH-HOAc
Ac2O-Py, rt,
10h
Ac2O-Py,
100°C, 4h
13
10
11
Fig. A
Fig. B

N-Tryptophyl-3-acetyl-1,2,5,6-tetrahydropyridine (5)

$LiAlH_4$ (60 mg, 1.5 mmol) was added to the quaternary iodide salt 4 (150 mg, 0.33 mmol) in dry THF (30 ml) under N_2. The reaction mixture was stirred at room temperature for 15 min, then refluxed for 3 h and cooled. The excess $LiAlH_4$ was decomposed by the addition of cold water. The solution was next treated with 6 N NaOH (5 ml) solution, filtered through celite and acidified with conc. HCl (7 ml). After stirring at room temperature for 45 min, it was basified with conc. NH_3 solution and extracted with $CHCl_3$ (2x50 ml). The organic solvent was dried (Na_2SO_4) and distilled off. The residue was purified by chromatography (silica gel) to afford 53 mg of 5 (61%), mp 188-190°C (MeOH) [lit.[10] mp 186-190°C (MeOH)]; ir ν_{max} : 3400, 1670 and 1650 cm^{-1}; ^1H nmr : δ 1.48-1.88 (m,1H), 2.28-2.44 (m,3H), 2.68-3.04 (m,4H), 3.12 (d,2H, J=2 Hz), 6.88-7.68 (m,6H) and 10.80 (s,1H); ms m/z (rel. intensity) : 268 (M^+, 55), 139(80), 138(80), 130(100).

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

The iodide salt 4 (450 mg, 1 mmol) was added in small portions to $(^tBuO)_3LiAlH$ (508 mg, 2 mmol) in dry THF (30 ml) at 0°C under N_2. After 30 min at rt, the mixture was refluxed for 1 h and then cooled to 0°C. $LiAlH_4$ (38 mg, 1 mmol) was thereafter added to the reaction mixture and the refluxing continued for another 2 h. The mixture was cooled, acidified with 6 N HCl (5 ml), stirred for 30 min, then basified with NH_3 solution and extracted with $CHCl_3$ (3x25 ml). The material obtained on removal of solvent was purified by column chromatography. Elution with $CHCl_3$-MeOH (49:1) yielded 118 mg of the amide 6, mp 146-147°C ($CHCl_3$-MeOH-Pet. ether) [lit.[8] mp 130-134°/170-180°C (MeOH)]; ir ν_{max} : 3240, 1635, 1625, 1595 and 1570 cm^{-1}; ^1H nmr : δ 1.54 (dt,1H, J=12 and 4 Hz), 2.04 (s,3H), 2.12-2.88 (m,5H), 3.36-4.08 (m,2H), 4.48 (br d,1H, J=10 Hz), 6.84-7.16 (m,2H), 7.20-7.56 (m,2H), 7.66 (s,1H) and 10.92 (s,1H); ms m/z (rel. intensity) : 266 (M^+, 100), 265 (M^+-1, 47), 251 (M^+-15, 15), 223 (M^+-43, 68), 169(20) and 156(63).

Lithium Aluminium Hydride Reduction of 6

The amide 6 (400 mg, 1.5 mmol) in dry THF (65 ml) was added to $LiAlH_4$ (170 mg, 4.5 mmol) in the same solvent (10 ml) under N_2 at 0°C. After addition the mixture was refluxed for 3 h. Usual work-up gave a gummy residue which on column chromatography (silica gel) using $CHCl_3$-MeOH (49:1) as the eluting solvent yielded compounds 7 (162 mg, 40%, mp 200-201°C), 8 (106 mg, 26%, mp 159-160°C), 9 (15 mg, 4%, mp 128°C) and minor quantities of 1 and its Z-isomer (0.5%).

When, however, the reduction was carried out at room temperature for 3 h using the tertiary amide 6 (225 mg, 0.8 mmol) and $LiAlH_4$ (68 mg, 1.8 mmol) in THF (60 ml), the yields of the various products were : 7 (15 mg, 7%), 8 (40 mg, 18%), 9 (31 mg, 14%) and 1 and its Z-isomer (0.8%).

Compound 7 : ir ν_{max} : 3480-3140, 2840 and 2780 cm^{-1}; ^1H nmr : δ 1.07 (d,3H, J=6 Hz), 1.28-2.20 (m,5H), 2.36-3.08 (m, 7H), 3.78 (m,1H), 4.48 (br s,1H), 6.76-7.10 (m,2H), 7.16-7.48 (m,2H) and 10.64 (s,1H); ^{13}C nmr :

δ 23.6 (t,C-1), 26.0 (t,C-2), 41.3 (d,C-3), 66.6 (d,C-1'), 21.7 (q,C-2'), 56.1 (t,C-4), 52.8 (t,C-6), 20.5 (t,C-7), 106.0 (s,C-7a), 126.8 (s,C-7b), 117.3 (d,C-8), 120.2 (d,C-9), 118.2 (d,C-10), 110.9 (d,C-11), 135.9 (s,C-11a), 135.5(s,C-12a) and 59.0 (d,C-12b); ms m/z (rel. intensity) : 270 (M^+, 86), 269 (M^+-1, 100), 225(46), 223(14), 197(15), 184(24), 171(24), 170(57), 169(53), 156(24) and 155(20).

Compound 8 : ir ν_{max} : 3248-3140, 2815 and 2765 cm^{-1}; ^1H nmr : δ 1.06 (d,3H, J=6 Hz), 1.14-3.16 (m,13H), 4.38 (br d,1H, J=5 Hz), 6.80-7.10 (m,2H), 7.16-7.46 (m,2H) and 10.62 (s,1H); ^{13}C nmr : δ 29.3 (t,C-1), 26.2, 26.9 (2xt,C-2), 43.2, 43.5 (2xd,C-3), 68.2, 68.6 (2xd,C-1'), 20.8, 21.1 (2xq,C-2'), 57.8, 58.2 (2xt,C-4), 53.1 (t,C-6), 21.6 (t,C-7), 106.2 (s,C-7a), 126.7 (s,C-7b), 117.3 (d,C-8), 120.1 (d,C-9), 118.1 (d,C-10), 110.9 (d,C-11), 136.0 (s,C-11a), 136.0 (s,C-12a) and 60.0 (d,C-12b); ms m/z (rel. intensity) : 270 (M^+, 71), 269 (M^+-1, 90), 225(64), 223(41), 197(31), 184(47), 170(90), 169(100), 156(64) and 155(98).

Compound 9 : ir ν_{max} : 3480, 2840, 2780 and 1700 cm^{-1}; ^1H nmr : δ 1.44 (m,2H), 2.14(s,3H), 2.18-3.24 (m,10H), 6.80-7.12 (m,2H), 7.16-7.48 (m,2H) and 10.68 (s,1H); ms m/z (rel. intensity) : 268 (M^+, 92), 267 (M^+-1, 98), 225(62), 223(71), 197(44), 184(67), 170(100), 169(95), 156(75) and 155(55).

Reduction of 6 with Lithium Aluminium Hydride - Aluminium Chloride (1:1)

The amide 6 (133 mg, 0.5 mmol) was added to a mixture of $LiAlH_4$ (57 mg, 1.5 mmol) and $AlCl_3$ (200 mg, 1.5 mmol) in diethyl ether (100 ml) at 0°C and refluxed for 3 h under N_2. Usual work-up followed by column chromatography with CH_2Cl_2-Pet. ether (1:1) furnished 1 (24 mg, 18%) and its Z-isomer (trace) which was purified by preparative TLC. (±)-Deplancheine 1 : mp 138-141°C (Et_2O/Pet. ether) [lit.[3] mp 139-142°C]; ir ν_{max}: 3480-3160, 2810 and 2755 cm^{-1}; ^1H nmr ($CDCl_3$) : δ 1.61 (d,3H, J=6.5 Hz), 1.78-2.28 (m,4H), 2.58-3.50 (m,7H), 5.44 (q,1H, J=6.5 Hz), 7.04-7.60 (m,4H) and 7.80 (br s,1H); ms m/z (rel. intensity) : 252 (M^+, 100), 251 (M^+-1, 66), 237 (M^+-15, 41), 223 (M^+-C_2H_5, 37), 169(34) and 156 (42).

Acetylation of 7 and 8

Compound 7 (23 mg, 0.08 mmol) in dry pyridine (2 ml) and acetic anhydride (0.4 ml) was heated on a water-bath for 4 h. After normal work-up, the product was purified by column chromatography over neutral alumina to furnish 11 (15 mg, 57%), mp 144-146°C (CH_2Cl_2/Pet. ether); ir ν_{max}: 3460-3140, 2820, 2760, 1730 and 1715 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.21 (d,3H, J=6.5 Hz), 2.05 (s,3H), 4.84 (m,1H), 7.04-7.58 (m,4H) and 7.75 (br s,1H); ms m/z (rel. intensity): 312 (M^+, 100), 311 (M^+-1, 95), 267(26), 251(26), 225(57), 223(38), 169(28), 156(19) and 155(30).

Compound 8 (25 mg, 0.09 mmol) was acetylated smoothly at rt to yield 10 (23 mg, 80%), mp 120-121°C ($CHCl_3$/Pet. ether) with shrinkage at 80°C; ir ν_{max}: 3340, 2805, 2780, 2750 and 1705 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.20 (d,3H, J=6.5 Hz), 1.97 (s,3H), 3.64 (br t,1H), 5.14 (m,1H), 7.04-7.54 (m,4H) and 7.73 (br s,1H); ms m/z

(rel. intensity): 312 (M^+, 100), 311 (M^+-1, 90), 267(26), 251(37), 225(71), 223(41), 197(20), 184(18), 170(30), 169(36), 156(28) and 155(17).

Conversion of 6 to 1 by Triethyloxonium Tetrafluoroborate and Sodium Borohydride

The amide 6 (133 mg, 0.5 mmol) in dry CH_2Cl_2 (5 ml) was added to triethyloxonium tetrafluoroborate (120 mg, 0.75 mmol) in the same solvent (1 ml) and stirred at room temperature for 2 h under N_2. The CH_2Cl_2 solution was evaporated, the residue dissolved in dry MeOH (5 ml), cooled to 0°C and $NaBH_4$ (80 mg, ~2 mmol) was added to it. The mixture was stirred at 0°C for 1 h and then at room temperature for another hour. Usual work-up followed by column chromatography on neutral alumina with pet. ether - ether (1:1) and subsequent preparative TLC afforded 1 (30 mg, 23%) and 12 (22 mg, 15%), mp 100-104°C (decomp.); ^{1}H nmr ($CDCl_3$): δ 1.22 (t,3H, J=6.5 Hz), 1.86 (s,3H), 7.04-7.60 (m,4H) and 7.80 (br s,1H); ms m/z (rel. intensity): 296 (M^+, 8), 295(7), 267(60), 265(42), 250(50), 223(46), 170(67), 169(60) and 156(100).

Preparation of p-Tosylhydrazone of 7

p-Tosylhydrazide (19 mg, 0.1 mmol) was added to a solution of ketone 9 (27 mg, 0.1 mmol) in a mixture of MeOH (1.5 ml) and AcOH (0.5 ml). After 5 h at rt the reaction mixture was basified with NH_3 solution and extracted with $CHCl_3$. The residue after evaporation of the solvent was crystallised with $CHCl_3$-Pet. ether to afford 13 (27 mg, 60%), mp 177-182°C (decomp.); ir ν_{max}: 3420-3230, 3180, 2825, 2760, 1635 and 1595 cm^{-1}; ^{1}H nmr : δ 1.80 (s,3H), 2.40 (s,3H), 7.02 (m,2H), 7.20-7.56 (m,4H) and 7.80 (d,2H, J=8 Hz).

Conversion of 13 to 1

Compound 13 (20 mg, 0.043 mmol) was dissolved in diglyme (2 ml) and heated with sodium methoxide (6 mg, 0.11 mmol) at 150°C for 1 h under N_2. The reaction mixture was poured into ice-water, extracted with $CHCl_3$ and the product was purified by preparative TLC to afford 1 (65%).

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