SYNTHESIS OF 3-ACETYL-1,4,6,7,12,12b-HEXAHYDROINDOLO[2,3-a]-QUINOLIZINE

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Abstract - A facile synthesis of the title compound (5), a key synthon for ajmalicine and related indole alkaloids, is described.

For an improved synthesis of ajmalicine, an antihypertensive agent, we sought a convenient method for the preparation of 3-acetyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (5), a key intermediate[1,2] used in the synthesis of several indole and oxindole alkaloids[3].

1-Ethoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (1), prepared from tryptamine and carboethoxypyruvic acid by modification of Kline's procedure[4], was smoothly reduced with lithium aluminium hydride to the corresponding alcohol (2). Michael reaction of the latter with methyl vinyl ketone afforded the keto-alcohol (3) in fairly good yield. Subsequent attempts to oxidise it [using dimethyl sulfoxide (DMSO) in combination with other reagents[5]] to the desired α,β-unsaturated ketone (5) through *in situ* cyclization of an intermediate keto-aldehyde not only failed but also led to retro-Michael reaction when acidic condition was employed. The oxidation with the commonly used chromium reagents[6] also proved ineffective due to precipitation of the reacting base possibly as chromium salts. Even the oxidative cyclization of the keto-alcohol (3) through tosylation followed by DMSO/$NaHCO_3$ treatment[7] proved equally unsuccessful. Nevertheless, the target compound (5) could be obtained in *ca.*26% yield under the same condition from the diol (4) prepared by sodium borohydride reduction of (3). The *trans* geometry[8] of the quinolizidine ring system was deduced from the Bohlmann bands at 2760 and 2810 cm^{-1} and the absence of any aliphatic proton signal downfield from δ3.7 in the ^1H nmr spectrum.

EXPERIMENTAL

Mps taken in open capillaries are uncorrected. ^{1}H nmr spectra were recorded on a JEOL FX-100 FT nmr spectrometer using tetramethylsilane as internal standard and mass spectra (EI) on a Hitachi RMU-6L instrument.

Preparation of 1-ethoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (1)

Carboethoxypyruvic acid (8 g, 50 mmol) in dry ethanol (25 ml) was added over a period of 8 h to a solution of tryptamine hydrochloride (6 g, 30 mmol) in the same solvent (150 ml) at 40°C under N_2. After the addition was over, the mixture was refluxed for 24 h, cooled and finally refrigerated overnight when the product crystallised out. Recrystallisation from methanol yielded (5.7 g, 65%) hydrochloride of 1 as needles, mp 242°C, lit[4]. mp 241-243°C.

Preparation of Alcohol 2

An ethereal solution (30 ml) of the free base liberated from the hydrochloride of 1 (2 g, 6.8 mmol) was added dropwise to lithium aluminium hydride (1.06 g, 28 mmol) in dry ether (20 ml) under N_2 and stirred at room temperature for 30 min. Usual work-up yielded alcohol 2 as a hygroscopic solid (1.32 g, 90%) ; ir ν_{max} (KBr) : 3400 (NH) and 3250 cm^{-1} (OH) ; ^{1}H nmr ($CDCl_3$) : δ 2.00 (q,2H, J = 5 Hz), 2.60 - 3.40 (m,6H), 3.84 (t,2H, J = 4 Hz), 4.30 (t, 1H, J = 5 Hz), 7.00 - 7.60 (m,4H) and 8.20 (s,1H); MS m/e(rel. intensity) : 216 (M^+)(11), 171 (100), 169 (49) and 156 (50).

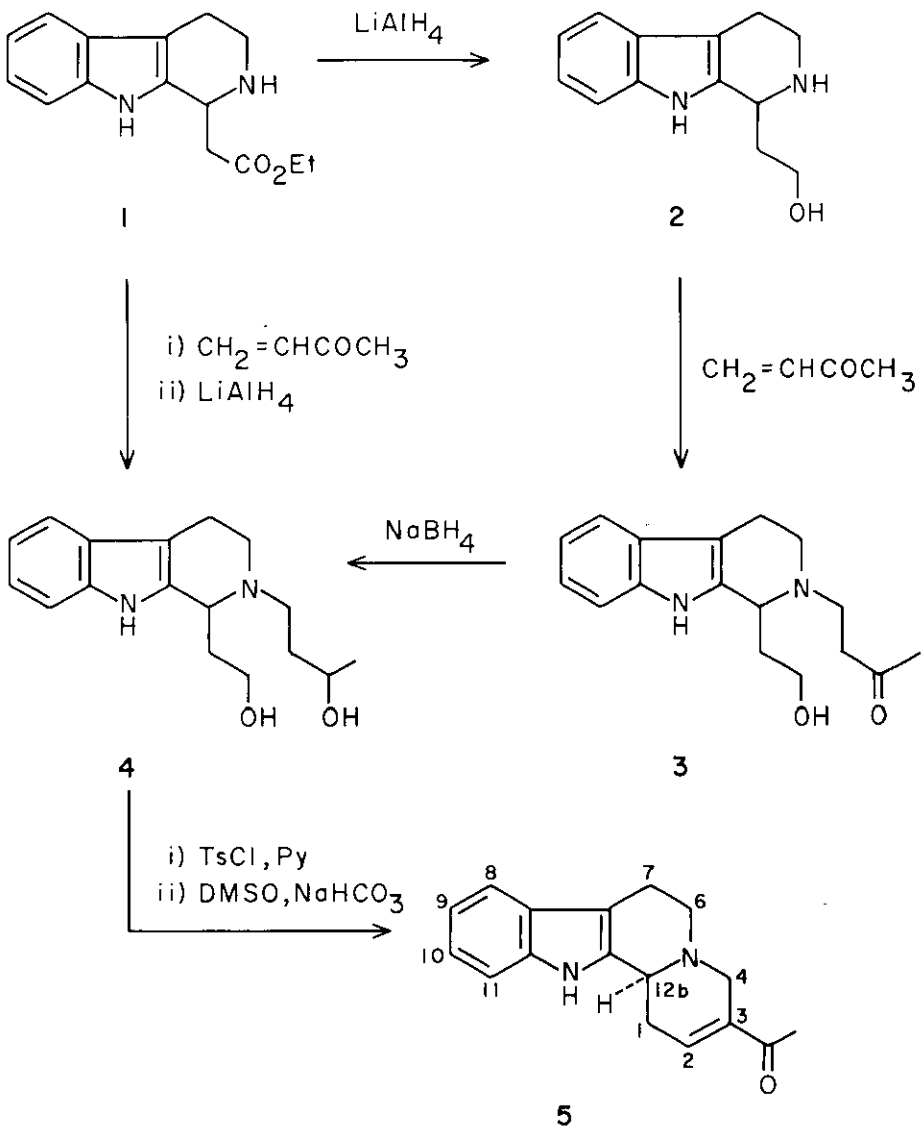
Preparation of Keto - alcohol 3

Freshly distilled methyl vinyl ketone (0.7 g, 10 mmol) in dry ethanol (2 ml) was added dropwise at room temperature to 2 (1.0 g, 4.6 mmol) in the same solvent (8 ml) under N_2 and the reaction mixture was kept at 0°C for 12 h. The gummy material obtained after solvent removal was crystallised from ether to furnish 3 (0.71 g, 54%), mp 128-130°C ; ir ν_{max} (KBr) : 3500-3100 (NH,OH) and 1705 cm^{-1} (CO) ; ^{1}H nmr ($CDCl_3$) : δ 1.96 (m, 2H), 2.16 (s, 3H), 2.60 - 3.40 (m,9H), 3.72 - 4.00 (m , 3H), 7.00 - 7.60 (m,4H) and 7.92 (s, 1H) ; MS m/e(rel. intensity) : 241 (M^+-C_2H_5O)(75), 171 (100), 170 (58), 169 (98) and 156 (83).

Preparation of Diol 4

Sodium borohydride (113 mg, 3 mmol) was added in small portions to 3 (300 mg, 1.05 mmol) in methanol (10 ml) at 10°C. The mixture was left for 1 h at room temperature. Usual work-up followed by short column chromatography (silica gel) afforded a gummy material (4) (273 mg, 85%) as a mixture (tlc) of two isomers ; ir ν_{max} (KBr) : 3650-3100 cm^{-1} (NH,OH) ; ^{1}H nmr ($CDCl_3$) : δ 1.23 and 1.25 (2 x d, 3H, J = 5.5 Hz), 1.72 (m,2H), 2.04 (m,2H), 2.60 - 3.60 (m,10H), 3.76 - 4.08 (m,4H), 7.00 - 7.60 (m,4H) and 8.45 and 8.52 (2 x s, 1H) ; MS m/e(rel. intensity) : 288 (M^+)(3), 244 (90), 243 (100), 215 (12), 171 (80), 170 (90), and 169 (90).

The same isomeric mixture was obtained in 12% overall yield by addition of methyl vinyl ketone to 1 in dry ethanol at 0°C and $LiAlH_4$ reduction of the product in refluxing THF under N_2.


LiAlH4
NH
N
H
CO2Et
1
2
OH
i) CH2=CHCOCH3
ii) LiAlH4
CH2=CHCOCH3
NaBH4
OH
OH
O
4
3
i) TsCl, Py
ii) DMSO, NaHCO3
8
7
9
6
10
N
4
11
H
12b
H
1
3
2
O
5

Preparation of α,β-Unsaturated Ketone 5

p-Toluenesulphonyl chloride (191 mg, 1 mmol) was added to the mixture of diol 4 (144 mg, 0.5 mmol) in dry pyridine (2 ml) at 10°C and left as such for 2 h. Usual work-up afforded the tosylate which was heated without further purification at 120-130°C in DMSO (2 ml) for 5 min under N_2, $NaHCO_3$ (100 mg) was then added and the temperature maintained for two more min. The solution was poured into ice-water and extracted with dichloromethane. The residue obtained after evaporation of the solvent was purified by chromatography (silica gel) to afford 5 (34 mg, 26%) ; mp 204-205°C (lit.[1] 205°C). The spectral data (ir, nmr, MS) were in excellent agreement with the reported values[1] for the compound.

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