

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

Sukhendu B. Mandal and Satyesh C. Pakrashi*

Indian Institute of Chemical Biology, Calcutta-700032, India

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 alkaloids³.

1-Ethoxycarbonylmethyl-1,2,3,4-tetrahydro- β -carboline (1), prepared from tryptamine and carboethoxypyruvic acid by modification of Kline's procedure⁴, was smoothly reduced with lithium aluminium hydride to the corresponding alcohol (2). Michael reaction of the latter with methylvinyl ketone afforded the keto-alcohol (3) in fairly good yield. Subsequent attempts to oxidise it [using dimethyl sulfoxide (DMSO) in combination with other reagents⁵] 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 reagents⁶ 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 treatment⁷ 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* geometry⁸ 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 $\delta 3.7$ in the ^1H nmr spectrum.

EXPERIMENTAL

Mps taken in open capillaries are uncorrected. ^1H 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 , lit⁴. mp $241\text{--}243^\circ\text{C}$.

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); ^1H nmr (CDCl_3): δ 2.00 (q, 2H, $\underline{J} = 5\text{ Hz}$), 2.60 - 3.40 (m, 6H), 3.84 (t, 2H, $\underline{J} = 4\text{ Hz}$), 4.30 (t, 1H, $\underline{J} = 5\text{ Hz}$), 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).

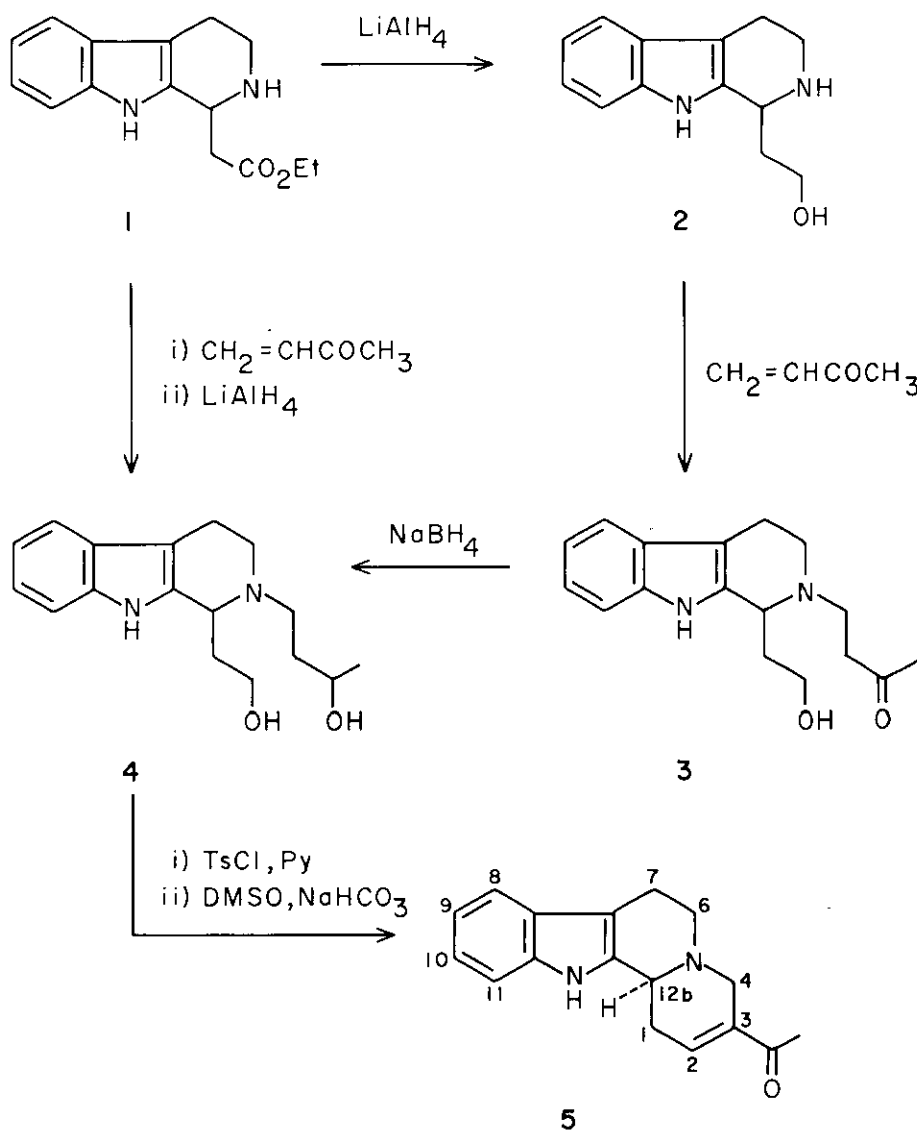
Preparation of Keto - alcohol 3

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 $128\text{--}130^\circ\text{C}$; ir ν_{max} (KBr): 3500-3100 (NH, OH) and 1705 cm^{-1} (CO); ^1H 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 ($\text{M}^+ - \text{C}_2\text{H}_5\text{O}$)(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): $3650\text{--}3100\text{ cm}^{-1}$ (NH, OH); ^1H nmr (CDCl_3): δ 1.23 and 1.25 (2 x d, 3H, $\underline{J} = 5.5\text{ Hz}$), 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 .



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 N₂, NaHCO₃ (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 values¹ for the compound.

REFERENCES

1. E. Winterfeldt, H. Radunz and T. Korth, Chem. Ber., 1968, 101, 3172.
2. M. Lounasmaa and M. Puhakka, Acta Chem. Scand., 1978, B 32, 77, 216.
3. E. Winterfeldt, A. J. Gaskell, T. Korth, H. Radunz and M. Walkowiak, Chem. Ber., 1969, 102, 3558 ; E. Winterfeldt and H. Riesner, J. Chem. Soc., Chem. Comm., 1972, 786 ; G. Benz, H. Riesner and E. Winterfeldt, Chem. Ber., 1975, 108, 248 ; G. Racker, M. Stahl, M. Walkowiak and E. Winterfeldt, ibid., 1976, 109, 3817.
4. G. B. Kline, J. Am. Chem. Soc., 1959, 81, 2251.
5. W. W. Epstein and F. W. Sweat, Chem. Rev., 1967, 67, 247 ; J. G. Moffatt, J. Org. Chem., 1971, 36, 1909 ; J. D. Albright, ibid., 1974, 39, 1977 ; D. H. R. Barton and C. P. Forbes, J. Chem. Soc., Perkin 1, 1975, 1614.
6. G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, J. Am. Chem. Soc., 1953, 75, 422 ; E. J. Corey and G. W. J. Fleet, Tetrahedron Lett., 1973, 4499 ; E. J. Corey and J. W. Suggs, ibid., 1975, 2647.
7. N. Kornblum, W. J. Jones and C. J. Anderson, J. Am. Chem. Soc., 1959, 81, 4113.
8. T. A. Crabb, R. F. Newton and D. Jackson, Chem. Rev., 1971, 71, 109.

Received, 21st December, 1984