A CONVENIENT METHOD FOR THE PREPARATION OF 3-ACETYL-1,2,3,4,6,7,12,12b-OCTAHYDROINDOLO[2,3-a]QUINOLIZIN-2-ONE, A KEY INTERMEDIATE FOR THE SYNTHESIS OF AJMALICINE

Bhim C. Maiti and Satyesh C. Pakrashi*

Indian Institute of Chemical Biology, Calcutta-700 032, INDIA

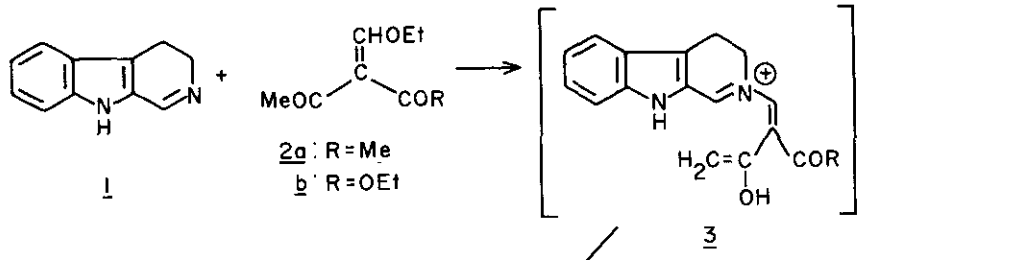
Abstract - Reaction of 3,4-dihydro-β-carboline (1) and 3,4-dihydroisoquinoline (7a-b) with ethoxymethyleneacetylacetone (2a) and ethyl ethoxymethyleneacetoacetate (2b) yielded new tetra- and tricyclic compounds (4a-b, 8a-d). The enaminone 4a on $NaBH_4$ reduction led to the title compound.

In connection with our programme of synthesis of some indole alkaloids with trans-quinolizine ring system, we required a convenient method for the preparation of 3-acetyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-one (5a), a key intermediate for the synthesis of ajmalicine[1] and a number of other heterocyclic bases. Herein we report an efficient two-step procedure to obtain 5a which has been prepared earlier[2] through a multi-step process with low overall yield.

Michael addition of 3,4-dihydro-β-carboline (1)[3] with ethoxymethyleneacetylacetone (2a)[4] or ethyl ethoxymethyleneacetoacetate (2b) in ethanol at room temparature afforded the tetracyclic products (4a or 4b) directly in ca. 90% yield. The attempted hydrogenation of the enaminone (4a) or of its perchlorate under different conditions furnished only a small amount (ca. 5-8%) of the desired dione (5a)[5]. The reduction could, however, be brought about with $NaBH_4$ in excellent yield. The α-axial orientation of 12b-H in 5a was supported from the observed (i) Bohlmann bands (sharp signals) in its i.r. spectrum and (ii) double doublet with J = 15.5 and 5.5 Hz for 12b-H in the n.m.r. spectrum of 4a.

We extended this method to the condensation of 3,4-dihydroisoquinolines (7a-b) with β-keto-ethoxymethylene derivatives (2a-b) to ascertain its general applicability. New tricyclic compounds (8a-d) could indeed be obtained in high yields (Table 1). Thus reduction of 8b with $NaBH_4$ gave 10 in 81% yield.

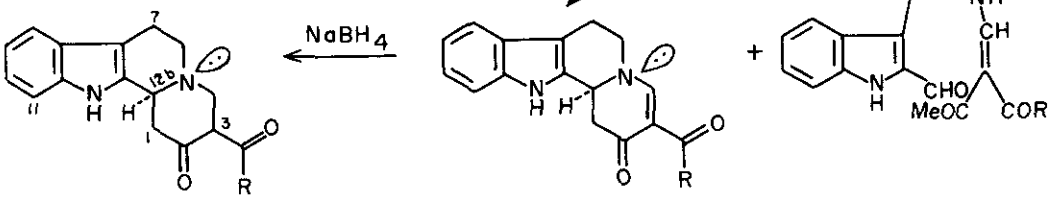
That the formation of 4 proceeds via the intermediacy of 3 became apparent from the isolation of the hitherto unknown indole-2-aldehyde derivatives (6a-b) as



1

2a : R = Me
b : R = OEt

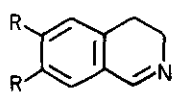
3



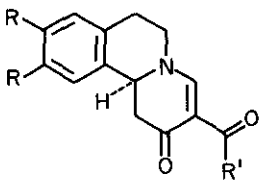
5a R = Me
b : R = OEt

4a . R = Me
b : R = OEt

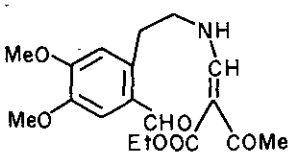
6a : R = Me
b : R = OEt



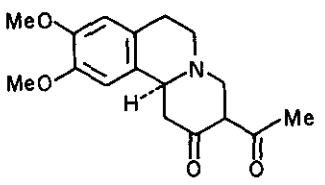
7a . R = H
b : R = OMe



8a . R = H, R' = Me
b : R = OMe, R' = Me
c : R = H, R' = OEt
d : R = OMe, R' = OEt



9



10

Table 1. Physical data of compounds (4-10)

Compd.	Yield (%)	m.p./°C/[a]	Mol. formula[b]	^{1}H NMR[c] δ (ppm)
4a	90	316-317 (A)	$C_{17}H_{16}N_2O_2$	2.34 (s, 3H), 2.58 (d, 1H), 2.80-3.12 (m, 3H), 3.46-3.82 (m, 1H), 4.16-4.42 (m, 1H), 5.16 (dd, 1H), 6.90-7.56 (m, 5H) and 8.48 (brs, 1H).
4b	88	305-306 (A)	$C_{18}H_{18}N_2O_3$	1.18 (t, 3H), 2.52 (m, 2H), 2.88 (m, 2H), 3.64 (m, 1H), 4.08 (q, 2H), 4.32 (m, 1H), 5.10 (dd, 1H), 6.96-7.54 (m, 4H), 8.40 (brs, 1H) and 8.96 (br, 1H).
5a[d,e]	86	212-213 (B)	$C_{17}H_{18}N_2O_2$	2.16 (s, 3H), 2.24-3.88 (m, 9H), 7.02-7.60 (m, 4H), 7.74 (br, 1H) and 15.60 (s, 1H).
5b[d,f]	78	165-166 (B)	$C_{18}H_{20}N_2O_3$	1.30 (t, 3H), 2.48-3.86 (m, 9H), 4.26 (q, 2H), 7.04-7.60 (m, 4H), 7.78 (br, 1H) and 12.02 (s, 1H).
6a	4	220 (A)	$C_{17}H_{18}N_2O_3$	1.84 (s, 3H), 2.18 (s, 3H), 3.20-3.52 (m, 2H), 3.64 (t, 2H), 6.94-7.90 (m, 5H), 9.90 (s, 1H), 10.70 (m, 1H) and 11.66 (brs, 1H).
6b	7	166 (C)	$C_{18}H_{20}N_2O_4$	1.07 (t, 3H), 2.27 (s, 3H), 3.16-3.56 (m, 2H), 3.63 (t, 2H), 3.97 (q, 2H), 6.99-7.90 (m, 5H), 9.87 (s, 1H), 10.83 (m, 1H) and 11.66 (brs, 1H).
8a	81	158-159 (C)	$C_{15}H_{15}NO_2$	2.54 (s, 3H), 2.67 (d, 1H), 2.81 (d, 1H), 2.92-4.04 (m, 4H), 4.94 (dd, 1H), 7.00-7.56 (m, 4H) and 8.42 (brs, 1H).
8b	85	196-197 (C)	$C_{17}H_{19}NO_4$	2.52 (s, 3H), 2.54-3.84 (m, 6H), 3.85 (s, 3H), 3.87 (s, 3H), 4.86 (dd, 1H), 6.60 (s, 1H), 6.67 (s, 1H) and 8.39 (brs, 1H).
8c	75	154 (C)	$C_{16}H_{17}NO_3$	1.32 (t, 3H), 2.43-4.10 (m, 6H), 4.29 (q, 2H), 4.94 (dd, 1H), 6.90-7.58 (m, 4H) and 8.34 (brs, 1H).
8d	79	194 (C)	$C_{18}H_{21}NO_5$	1.32 (t, 3H), 2.40-4.06 (m, 6H), 3.86 (s, 3H), 3.90 (s, 3H), 4.28 (q, 2H), 4.88 (dd, 1H), 6.62 (s, 1H), 6.67 (s, 1H) and 8.30 (brs, 1H).
9	5	108 (C)	$C_{18}H_{23}NO_6$	1.26 (t, 3H), 2.44 (s, 3H), 3.28 (t, 2H), 3.48 (t, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 4.16 (q, 2H), 6.66 (s, 1H), 7.30 (s, 1H), 7.79 (d, 1H), 10.00 (s, 1H) and 10.48 (m, 1H).
10[d]	81	177-178 (C)	$C_{17}H_{21}NO_4$	2.12 (s, 3H), 2.32-3.80 (m, 9H), 3.82 (s, 3H), 3.84 (s, 3H), 6.56 (s, 1H), 6.58 (s, 1H) and 15.56 (s, 1H).

[a]Recrystallisation solvent; A: ethanol; B: methanol; C: chloroform-petroleum ether; [b]All compounds gave satisfactory microanalyses; [c]Solvent d_6 DMSO for 4a-b and $CDCl_3$ for 5-10; [d]Compounds 5b-c and 10 exist, in solution, as the enol tautomers; [e]lit.[2] mp 205-206°; [f]lit.[6] mp 164-165°.

minor products (4-7%) when the condensation was carried out in the aqueous rather than in absolute ethanol. The aldehyde 9 obtained under the same condition from 8d implied that similar mechanism operates in the isoquinoline series as well.

Since ethoxymethyleneacetylacetone or ethyl ethoxymethyleneacetoacetate can also be readily prepared, the above method provides a useful synthetic route for β-carboline or benzoquinolizidine bases.

EXPERIMENTAL

Mps are uncorrected. ^{1}H NMR spectra were recorded on a *Jeol FX-100 FT* NMR spectrometer using TMS as internal standard and mass spectra (EI) on a Hitachi RMU-6L instrument.

General procedure for a synthesis of 4 and 8. Typically 3,4-dihydro-β-carboline (1.5 g, 0.03 mole) in dry ethanol (250 ml) was stirred under N_2 and a solution of ethoxymethyleneacetylacetone (5.45 g, 0.035 mole) in dry ethanol (50 ml) was added slowly. The solid separated after 4 h was filtered and crystallised to furnish 4a.

In cases of isoquinolines a reflux temperature for 4 h was maintained and the products were purified by short column chromatography (silica gel).

$NaBH_4$ reduction of enaminone 4 and 8b. $NaBH_4$ (3 x 50 mg) was added at an interval of 2 h to a solution of enaminone (5 mmole) in ethanol (300 ml) and the reaction mixture was stirred and monitored (tlc) for a total period of 6 h. Usual work up followed by crystallisation yielded the saturated dione.

REFERENCES AND NOTES

1. E. Winterfeldt, A. J. Gaskell, T. Korth, H.-E. Radunz and M. Walkowiak, Chem. Ber., 1969, 102, 3558.
2. K. B. Prasad and G. A. Swan, J. Chem. Soc., 1958, 2045.
3. N. Whittaker, J. Chem. Soc., 1969, 85.
4. L. Crombie, D. E. Games and A. W. G. James, J. Chem. Soc. Perkin I, 1979, 464.
5. The difficulty in the hydrogenation of enaminones either under normal or forcing conditions have also been reported by earlier workers (J. V. Greenhill, Chem. Soc. Rev., 1977, 6, 277; N. K. Kochetkov, Bull. Akad. Sci. USSR Div. Chem. Sci., 1954, 37; J. C. Martin, K. R. Barton, P. G. Gott, and R. H. Meen, J. Org. Chem., 1966, 31, 943; J. V. Greenhill, M. Ramli and T. Tomassini, J. Chem. Soc. Perkin I, 1975, 588).
6. G. B. Kline, J. Am. Chem. Soc., 1959, 81, 2251.

Received, 4th May, 1984