CONVENIENT SYNTHESIS OF 6,7-DIHYDROFLAVOPEREIRINE AND FLAVOPEREIRINE

Venkatachalam S. Giri, Bhim C. Maiti and Satyesh C. Pakrashi*

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

Abstract - The alkaloids 6,7-dihydroflavopereirine (9) and flavopereirine (10) have been synthesised from 3-acetyl-4-oxo-6,7-dihydro-12H-indolo-/2,3-a/quinolizine (5) obtained in one step by condensation of 1-methyl-3,4-dihydro-β-carboline (3) and ethyl ethoxymethyleneacetoacetate (4).

In connection with the syntheses of the novel zwitterionic alkaloids, viz. vincarpine (1) and dihydrovincarpine (2) isolated[1] from Vinca elegantissima in our laboratory, we have achieved a one-pot synthesis of 3-acetyl-4-oxo-6,7-dihydro-12H-indolo/2,3-a/quinolizine (5), a potential key intermediate for the syntheses of several indole alkaloids. Herein we report the syntheses of flavopereirine (10)[2-5] and 6,7-dihydroflavopereirine (9)[6] from 5.

Although a number of syntheses[7-17] of 9 and 10 are already known, this elegant synthesis with much higher yield appears to be the method of choice for the preparation of flavopereirine (10) in view of its recently observed[18] property of selective inhibition of in vitro synthesis of cancer DNA.

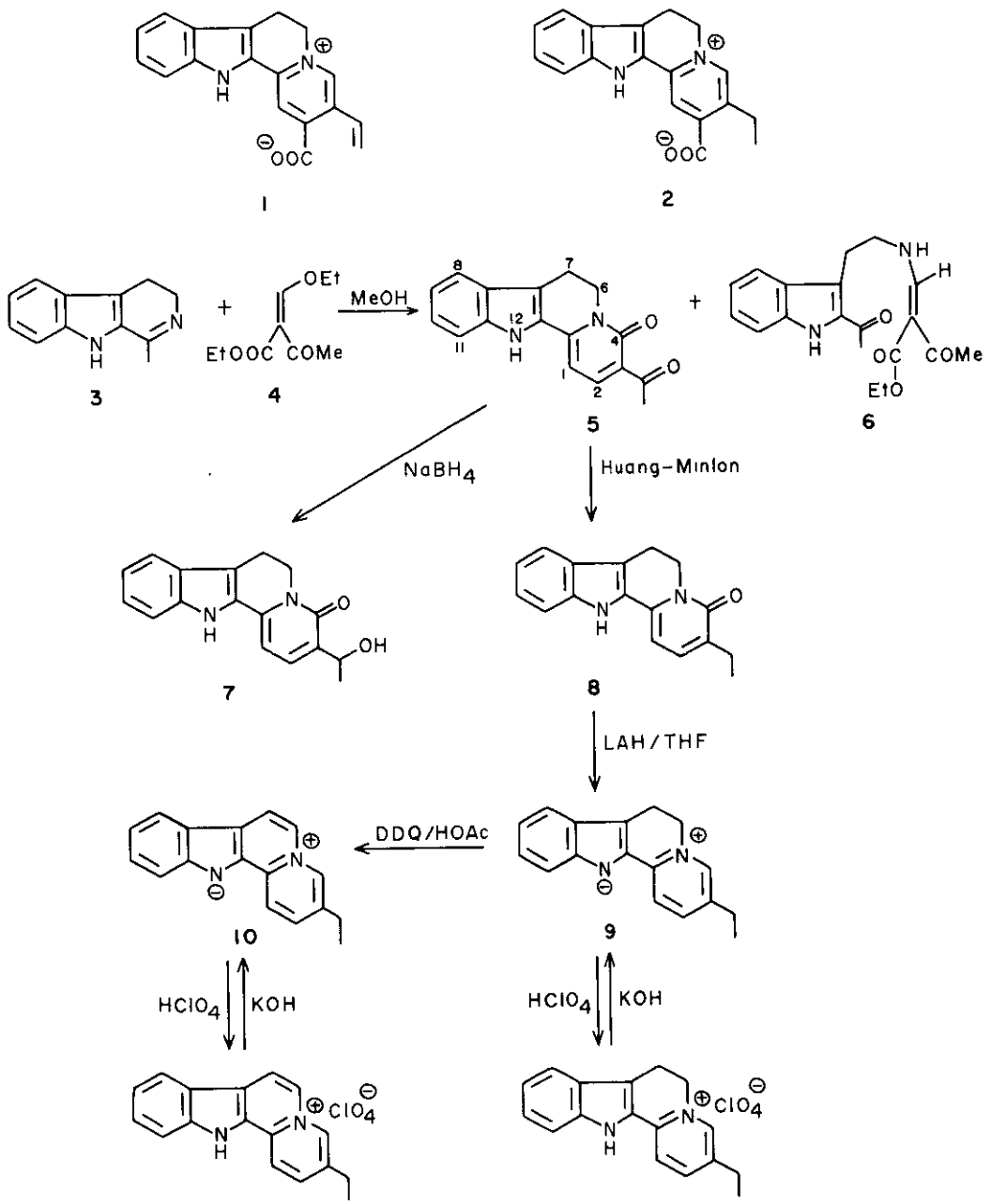
Condensation of 1-methyl-3,4-dihydro-β-carboline (3)[19] and ethyl ethoxymethylene-acetoacetate (4)[20] in dry MeOH at room temp. for 24 h gave[21] the desired compound 5 /60%, mp 271-272°C; ir (Nujol) : 3230, 1656 and 1640 cm^{-1}; uv(log ε): λ_{max} (MeOH) 253(3.53), 261(3.55), 274(3.27), 281(3.04), 318(3.17) and 426 nm (4.16); nmr ($CDCl_3$): δ 2.76(3H,s, COMe), 3.18(2H,t,J = 7 Hz,H-7), 3.52(2H,t,J = 7 Hz,H-6), 6.44(1H,d,J = 7.5 Hz,H-1), 7.12-7.48(3H,m,Ar-H), 7.64(1H,d,J = 8 Hz,H-8), 8.22 (1H,d,J = 7.5 Hz, H-2) and 8.38(1H,br,NH); ms m/z (rel. int.): 278(M^+, 44.5), 263(100), 235(12.8), 206(30.7) and 205(29)/ along with compound 6 /9%, mp 172-173°C; ir (Nujol): 3240, 1690, 1658 and 1640 cm^{-1}; nmr ($CDCl_3$): δ 1.23 (3H,t,J = 7 Hz), 2.40(3H,s), 2.57(3H,s), 3.43(2H,t,J = 7 Hz), 3.65(2H,t,J = 7 Hz), 4.12(2H,q,J = 7 Hz), 7.12-7.48(4H,m), 7.53-7.85(1H,m) and 8.92(1H,br); ms m/z (rel. int.): 342(M^+,32), 297(18.4), 278(17.6), 263(34), 185(45), 173(100) & 170(76).

$NaBH_4$ reduction of compound 5 yielded the expected alcohol 7 /95%, mp 227-229°C;

ir (Nujol): 3450-3200, 1645 and 1580 cm^{-1}; uv(log ε): λ_{max}(MeOH) 247(4.13), 256(4.16), 272(4.07), 284(4.06), 348(4.25), 366(4.54) and 386 nm (4.87); nmr (DMSO-d_6): δ 1.28(3H,d,J = 7 Hz, CHMe), 3.02(2H,t,J = 7 Hz,H-7), 4.30(2H,t,J = 7 Hz, H-6), 4.80(1H,m,CHMe), 4.98(1H,d,J = 6 Hz,CHOH), 6.68(1H,d,J = 7.5 Hz,H-1), 6.94-7.70(5H,m,Ar-H and H-2), and 11.54 (1H,br,NH); ms m/z (rel. int.): 280(M^+, 12.8), 265(88), 262(100), 247(80) and 233(89.6) [7]. Tosylation of 7 not being promising, our initial plan to prepare compound 8 through this intermediate had to be abandoned. However, Huang-Minlon reduction of 5 in refluxing diethylene glycol for 8 h furnished in about 80% yield the compound 8 [mp 259-260°C; ir(Nujol): 3230, 1640 and 1580 cm^{-1}; uv (log ε): λ_{max}(MeOH) 249(4.24), 258(4.25), 276(4.20), 284(4.19), 288(4.21), 350(4.52), 365(4.60) and 383 nm(4.54); nmr(DMSO-d_6): δ 1.12 (3H,t,J = 7 Hz,Et), 2.46(2H,q,J = 7 Hz,Et), 3.02(2H,t,J = 7 Hz, H-7), 4.32(2H,t,J = 7 Hz,H-6), 6.61(1H,d,J = 7.5 Hz,H-1), 7.32(1H,d,J = 7.5 Hz, H-2), 6.96-7.60(4H,m,Ar-H) and 11.52(1H,br,NH); ms m/z (rel. int.) : 264(M^+, 75.6), 249(100),235(8.1), 221(20.8), 219(29.7) and 206(20.5) [7].

$LiAlH_4$ reduction of compound 8 in refluxing THF with TLC monitoring (4 h) and usual work up gave a yellow crystalline compound having all the properties of 6,7-dihydro-flavopereirine 9 [34%, mp 305-307°C(dec.); ir (Nujol) : 3340, 1630, 1590 and 1555 cm^{-1}; uv (log ε): (a) λ_{max}(MeOH) 251(3.84), 313(4.13) and 391 nm(4.11). (b)λ_{max} (MeOH-KOH) 250(3.85), 263(3.71), 316(4.04), 360(4.03) and 405 nm(4.10); nmr(DMSO-d_6): δ 1.28(3H,t,J = 7 Hz,Et), 2.80 (2H,q,J = 7 Hz,Et), 3.32(2H,t,J = 7 Hz,H-7), 4.88(2H,t,J = 7 Hz,H-6), 7.06-7.76(4H,m,Ar-H), 8.36(2H,m,H-1 and H-2), 8.92(1H,s,H-4) and 12.66(1H,br,NH); ms m/z (rel. int.): 248(M^+, 40.6), 247(100), 232(25.4), 219(18.6) and 204(11.5) [7], the perchlorate of which had mp 281-282°C(lit.[12] 278-281°C).

Oxidation of 9 with DDQ in HOAc for 3 h at 100°C yielded flavopereirine (10), isolated as its perchlorate [mp 317-318°C(dec.), lit.[3] 316-317°C(dec.); ir(Nujol):3230,1630 and 1570 cm^{-1}; uv(log ε):(a) λ_{max}(MeOH) 233(4.58), 244(4.50), 288(4.22), 318(4.21), 348(4.33) and 388 nm(4.23). (b) λ_{max}(MeOH-KOH) 238(4.45), 252(4.24), 285(4.50), 313(4 13) and 360 nm(4.35); nmr(DMSO-d_6): δ 1.36(3H,t,J = 7 Hz,Et),2.96(2H,q,J = 7 Hz,Et), 7.36-7.92(3H,m),8.32-8.50(2H,m),8.72-9.04(3H,m),9.30(1H,s,H-4) and


1
2
3
4
MeOH
5
6
NaBH4
Huang-Minlon
7
8
LAH/THF
DDQ/HOAc
9
10
HClO4
KOH
HClO4
KOH

13.32(1H,br,NH); ms m/z (rel. int.): 246(M^+, 100) and 231 (42)_7 in 81% yield.

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