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SYNTHESIS OF 5-HYDROXYMETHYL-11-METHYL-6H-PYRIDO[4,3-b]CARBAZOLE AND 5-FORMYL-11-METHYL-6H-PYRIDO[4,3-b]CARBAZOLE (17-OXOELLIPTICINE)

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Abstract: A synthesis of 5-hydroxymethyl-11-methyl-6H-pyrido[4,3-b]carbazole and the corresponding 5-formyl derivative, 17-oxoellipticine,[3] is described, the key feature of which is the use of the Krohnke[1] aldehyde synthesis to effect the debenzylation of a p-nitrobenzyl-pyridinium salt under mild conditions.

The need arose for substantial quantities for biological testing of 5-hydroxymethyl-11-methyl-6H-pyrido[4,3-b]carbazole (6) which necessitated the development of a practical synthesis for this compound. Of all the syntheses[1] developed for ellipticine and its congeners, those of Weller[2] and Gribble[3] appeared to be the most amenable for adaptation to the preparation of 6. We now report a synthesis of 6 based on a modification of the Weller ellipticine synthesis.[2] The scheme used is shown in Fig. 1.

The methiodide 2 was prepared from 1 as described by Weller.[2] In our hands conditions necessary to effect demethylation with sodium thiophenoxide[2] were too drastic to permit the carbomethoxy group to survive unchanged. The benzyl bromide derivative 3[4,5] was prepared in an analogous manner with the hope that it could be removed more easily. Attempted hydrogenolysis of the benzyl group using conditions described by Pandit[6] and Brossi[7] for similar reactions led predominantly to the 1,2,3,4-tetrahydro derivative 9.[6,7] Debenzylation by careful heating of 3 in the presence of palladium or by reaction with various sulfur nucleophiles such as potassium ethylxanthate[8] and thiourea[9] proved unsatisfactory also.

The p-nitro analog 4[10] was prepared from 1 in 80% yield by treating the p-nitrobenzyl bromide salt of 1 with CH_3ONa, followed by addition of the methobromide of ethyl nicotinate to the reaction mixture.[2] When 4 was allowed to react with nitrosodimethylaniline for 5 h at 25°C in the presence of CH_3ONa in $CHCl_3$-MeOH the ester 5[11] was obtained in 47% yield after chromatography and crystallization.[12] This procedure is the one used by Krohnke[13] to prepare aldehydes from benzyl pyridinium salts. The desired ester 5 was accompanied by a difficultly

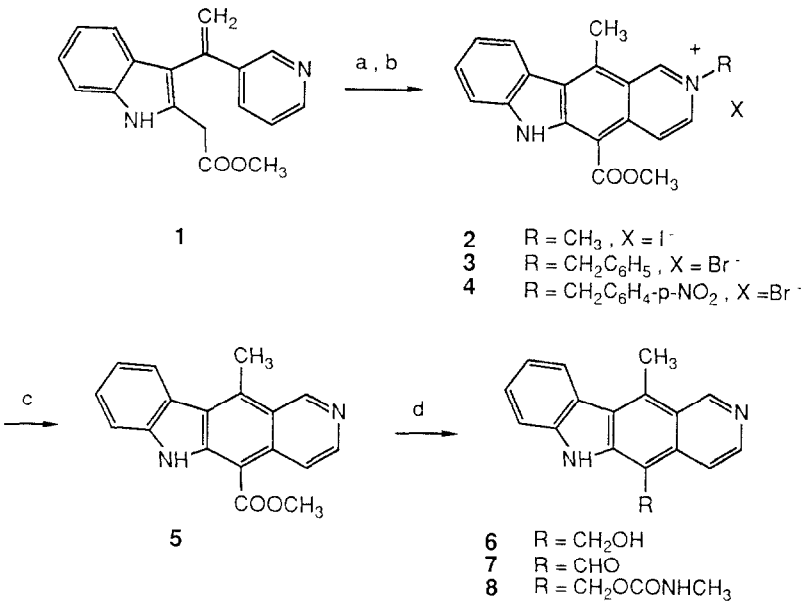
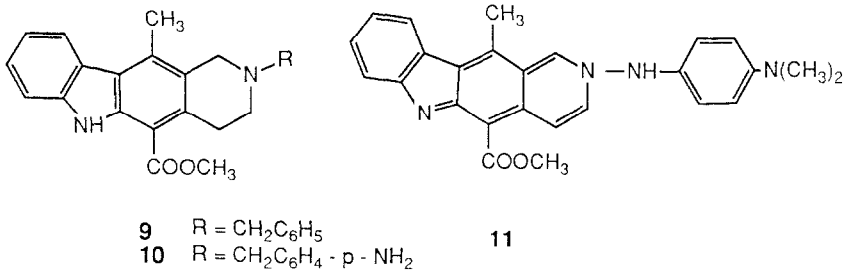


Fig. 1. a = RX; b = CH_3ONa; c = $(CH_3)_2NC_6H_4NO$; d = $LiAlH_4$



separable red by-product, the elemental analysis and NMR spectrum of which suggested that it was an adduct, derived fromo 5 and nitrosodimethylaniline, for which we tentatively assign structure 11.[14]

Reduction of crude 5 with LAH gave the desired alcohol 6[15] in 56% yield based on 4. The nitro analog 4 also underwent hydrogenolysis in the presence of palladium on charcoal to afford 5 in 30% yield; the remainder of the product was the tetrahydroamino analog 10. Oxidation of 6 with MnO_2 gave 7 in 79% yield based on starting material consumed (mp

270-272°C, lit.[3] mp 266-268°C), an alkaloid known as "17-oxoellipticine" previously synthesized by Gribble.[3] The IR spectrum of 7 was identical with that of an authentic sample.[3] $NaBH_4$ reduction of 7 returned 6. The N-methyl carbamate 8[16] was prepared in 61% yield by treating 7 with CH_3NCO in acetone-pyridine solution.

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Notes and References

1) For two excellent recent reviews of ellipticine alkaloids and related compounds, see G. W. Gribble and M. G. Saulnier, Heterocycles, 23, 1277 (1985) and M. Suffness and G. A. Cordell, The Alkaloids Vol. XXV, A. Brossi Ed., Academic Press, Inc., 1985, pps. 92-141.

2) D. D. Weller and D. W. Ford, Tetrahedron Lett., 25, 2104 (1984).

3) M. G. Saulnier and G. W. Gribble, Tetrahedron Lett., 24, 3831 (1983). An improved synthesis of 17-oxoellipticine was published recently by Obaza-Notatis and G. W. Gribble, J. Nat. Prod., in press (1986). We thank Professor Gribble for a pre-print of this paper and also for comparing the IR spectrum of 7 with that of an authentic sample.

4) Satisfactory elemental analyses were obtained for all new compounds described. Melting points taken on a Mel-Temp apparatus and are corrected.

5) m.p. 260-262°C (dec). IR (KBr) 3150, 3045, 2940, 1690, 1590, 1415 cm^{-1}. 200 MHz ^1H NMR (d_6-DMSO) δ 12.07 (s,1H) , 10.63 (s, 1H) , 9.22 (d, 1H), 8.60 (d, 1H) , 8.44 (d, 1H) , 7.82 (d, 1H), 7.68-7.20 (m, 7H), 5.94 (s, 2H), 4.02 (s, 3H), 3.34 (s, 3H).

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7) G. Grethe, H. L. Lee, M. Uskokovic and A. Brossi, J. Org. Chem., 33, 494 (1968).

8) A. R. Katritzky, U. Gruntz, N. Mongelli and M. C. Rezendi, J. Chem. Soc. Perkin I, 1953 (1979).

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10) m.p. 284-289°C (dec). IR (KBr) 3240, 3045, 2945, 1715, 1590, 1420 cm^{-1}. 200 MHz ^1H NMR (d_6-DMSO) δ 12.13 (s, 1H), 10.46 (s, 1H), 9.31 (d, 1H), 8.69 (d, 1H), 8.49 (d, 1H), 8.33 (d, 2H), 7.86 (m, 3H), 7.7-7.65 (m, 1H), 7.50-7.47 (m, 1H), 6.20 (s, 2H), 4.13 (s, 3H), 3.41 (s, 3H).

11) m.p. 203-204°C (dec). IR (KBr) 3300, 2950, 1675, 1600, 1465 cm^{-1}. 200 MHz ^1H NMR (d_6-DMSO) δ 11.50 (s, 1H), 9.73 (s, 1H) , 8.87 (d, 1H), 8.53 (d, 1H), 8.38 (d, 1H), 7.80 (d, 1H) , 7.60-7.52 (m, 1H), 7.36-7.29 (m, 1H), 4.10 (s, 3H), 3.33 (s, 3H).

12) The benzyl analog 3 failed to react under these conditions.

13) F. Krohnke, Chem. Ber., 71, 2583 (1938).

14) m.p. 241°C (dec.). IR (KBr) 2950, 1700, 1560, 1360, 1245, 1190 cm^{-1}. 200 MHz ^1H NMR (d_6-DMSO) δ 10.05 (s, 1H), 9.85 (s, 1H), 8.85 (d, 1H), 8.55 (d, 1H), 8.10 (d, 1H), 7.81 (d, 1H), 7.62 (d, 2H), 7.40-7.25 (m, 1H), 6.89 (d, 2H), 4.14 (s, 3H), 3.34 (s, 3H), 3.03 (s, 6H).

15) m.p. 257-258°C (dec). IR (KBr) 3380, 3090, 1600 cm^{-1}. 200 MHz ^1H NMR (d_6-DMSO) 11.46 (s, 1H), 9.71 (s, 1H), 8.43 (d, 1H), 8.39 (d, 1H), 8.08 (d, 1H), 7.62-7.48 (m, 2H), 7.30-7.22 (m, 1H), 5.25 (m, 3H), 3.32 (s, 3H).

16) m.p. 213-214.5°C (dec). IR (KBr) 3305, 1685, 1415, 1260, 1240 cm^{-1}. 100 MHz ^1H NMR (d_6-DMSO) δ 11.62 (s. 1H), 9.72 (s, 1H), 8.46 (d, 1H), 8.39 (d, 1H), 7.97 (d, 1H), 7.61-7.54 (m, 2H), 7.32-7.28 (m, 1H), 7.04 (d, 1H), 5.77 (s, 2H), 3.34 (s, 3H), 2.60 (s, 3H).

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