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SYNTHESIS OF 5-METHYL-6H-PYRIDO[4,3-b]CARBAZOLE-11-METHANOL

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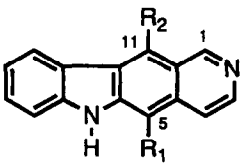
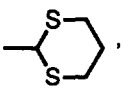
Summary: The structures of some of the intermediates in Saulnier-Gribble synthesis of ellipticine have been determined. One of the intermediates **8** has been converted to 5-methyl-6H-pyrido[4,3-b]carbazole-11-methanol, an alkaloid isolated from *Strychnos dinklagei* .

The alkaloid ellipticine (1, 5,11-dimethyl-6H-pyrido[4,3-b]carbazole) has generated considerable interest as a result of its antitumor properties in animals and humans.[1] In a previous paper[2] we reported the synthesis and antitumor activity of 11-methyl-6H-pyrido[4,3-b]carbazole 5-methanol-N-methylcarbamate 2 and suggested a mechanism to account for the antitumor activity of ellipticine which differed from the one proposed by Auclair and Paoletti.[3] In our suggested mechanism we postulated that the methyl group at C-5 in ellipticine is the site of metabolic activation. However there was no compelling evidence to rule out activation at the alternate C-11 methyl group.



1. $R_1 = R_2 = CH_3$ (ELLIPTICINE)
2. $R_1 = CH_2OOCNHCH_3$, $R_2 = CH_3$
3. $R_1 = CH_3$, $R_2 = CH_2OH$

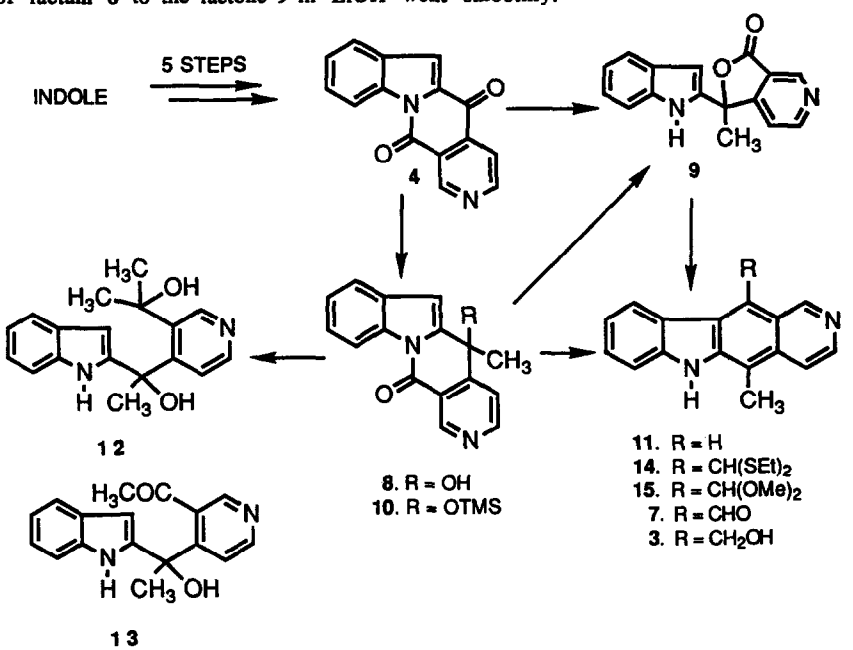


5. R_1 = , $R_2 = CH_3$
6. $R_1 = CHO$, $R_2 = CH_3$
7. $R_1 = CH_3$, $R_2 = CHO$

Koch et al.[4] isolated ten alkaloids from the stem bark of *Strychnos dinklagei.* Among them were four known 6H-pyrido[4,3-b]carbazoles including ellipticine 1 and four new ones. Of particular interest was 5-methyl-6H-pyrido[4,3-b]carbazole-11-methanol 3, which was present in very small quantities and obtained as a non-crystalline solid. It was characterized by means of a high resolution mass spectrum which furnished the correct empirical formula and an NMR spectrum run on a Bruker 270 MHz instrument. Suffness and Cardell[1] suggested that this compound be evaluated for anticancer activity, but up to the present time insufficient quantities have been available for testing from natural sources. In this communication we report the total synthesis of the alkaloid 3.

A number of methods are available for the synthesis of ellipticine and many of its analogs.[1,5] However, functionalization at C-11 position of ellipticine has not been reported. In 1982, Saulnier and Gribble[6] reported a synthesis of ellipticine utilizing the ketolactam 4, which was obtained from indole in five steps. The versatility of this ketolactam has been illustrated in the synthesis of

several dialkyl substituted pyrido[4,3-b]carbazoles.[7] For example, treatment of the ketolactam **4** with 1 equivalent of 2-lithio-2-trimethylsilyl-1,3-dithiane followed by 1 equivalent of methyllithium afforded a tertiary alcohol which was immediately reduced with $NaBH_4$ (EtOH, reflux) to give the corresponding C-5 dithiane **5**, which on hydrolysis gave 5-formyl norellipticine **6**. Addition of first, vinyllithium and second, methyllithium to the dione **4** followed by reduction with $NaBH_4$ gave 5-vinyl-11-methyl-6H-pyrido[4,3-b]carbazole which on careful oxidation afforded the aldehyde **6**.[8] Our attempts to reverse the above order of addition of the organolithium reagents did not furnish the desired precursor of 11-formyl ellipticine **7**. However we found that when the dione **4** was treated with 1 equivalent of methyllithium at -65°C and the reaction was quenched at +10°C with solid ammonium chloride, the lactam carbinol **8** was obtained as the major product.[9] When the above reaction mixture was quenched with water instead of solid ammonium chloride, the LiOH produced hydrolyzed lactam **8** to give the lactone **9** in 65% yield after acidic workup.[10] Conversion of lactam **8** to the lactone **9** in LiOH went smoothly.



Similarly treatment of the dione **4** with one equivalent of MeLi followed by trimethylsilyl chloride *in situ* gave the TMS ether **10**.[11] Both **8** and **9** on reduction with $NaBH_4$ (EtOH, reflux) gave 11-norellipticine **11** in 60-70% yield. Treatment of lactone **9** with methyllithium at 0°C for 2 hrs followed by $NaBH_4$ in refluxing ethanol for 8 hrs gave ellipticine **1** in almost quantitative yield. However when the lactam **8** was subjected to the same reaction conditions, two products were isolated. The minor product was ellipticine (10-15%) and the major product was diol **12**. The structure of the diol **12** was determined by NMR, and MS data.[12] The formation of the tertiary

carbinol **12** is the first direct evidence that **13** is an intermediate in the Saulnier-Gribble synthesis of ellipticine as suggested by these authors.[6] The isolation of lactam **8** in the high yield is evidence that it is the first intermediate in the Saulnier-Gribble synthesis of ellipticine.[6]

The lactone **9** proved to be a very useful compound for introducing functionality at the C-11 position of ellipticine.[13] After a number of unsuccessful attempts to add aldehyde equivalents such as 2-lithio-1-trimethylsilane-1,3-dithiane,[14] or lithio derivative of formaldehyde diethylmercaptal monosulfoxide[15] to **8**, **9**, or **10**, we were successful in condensing **9** and **10** with the lithio derivative of formaldehyde diethylmercaptal[16] to give, after reduction with $NaBH_4$ (EtOH, reflux) and flash chromatography, the mercaptal **14** in 25-35% yield.[17] All attempts to hydrolyze compound **14** with mercury chloride-mercuric oxide[18], perchloric acid[15a], mercuric chloride-cadmium carbonate[19], formic acid[16], NBS[20], NCS-$AgNO_3$[21], $AgNO_3$-EtOH[22] failed or gave intractable mixtures. When **14** was treated with four equivalent of bis(trifluoroacetoxy) iodobenzene[23] in aqueous acetonitrile (1:9)[24] at room temperature 11-formylellipticine **7** was obtained in 80% yield after chromatography.[25] Reduction of **7** with 5 equivalents of sodium cyanoborohydride and a few drops of CF_3COOH in absolute ethanol at room temperature gave 11-hydroxymethyl-5-methyl-6H-pyrido[4,3-b]carbazole **3** in almost quantitative yield. After column chromatography the compound was obtained as a yellow crystalline solid, mp 312-320°C, whose NMR spectrum was essentially identical with that reported by Koch and his colleagues.[4] The infrared and mass spectrum were in accord with the assigned structure.[26,27]

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References:

1. M. Suffness; G. A. Cardell, The Alkaloids; Brossi, A., Ed.; Academic Press; New York, 1985; Vol. XXV, page 89-142.
2. S. Archer; B. S. Ross; L. Pica-Mattoccia, D. Cioli, J. Med. Chem., 30, 1204 (1987).
3. C. Auclair; C. Paoletti, J. Med. Chem., 24, 280 (1981).
4. S. Michael, F. Tillequin, M. Koch, J. Nat. Prod., 45, 489 (1982); NMR(DMSO-d_6) δ 11.33(1H, s, NH), 9.70(1H, s, H_1), 8.33(2H, m, H_3, H_{10}), 7.88(1H, m, H_4), 7.44(2H, m, H_7, H_9), 7.15(1H, t, J=8Hz, H_8), 5.48(2H, s, CH_2), 5.44(1H, s, OH), 2.73(3H, s, CH_3)
5. M. Sainsbury, M. Synthesis, 437 (1977).
6. M. G. Saulnier; G. W. Gribble, J. Org. Chem., 47, 2810, (1982).
7. M. G. Saulnier; G. W. Gribble, Tet. Letters., 24, 3831 (1983).
8. J. A. Obaza-Nutaitis; G. W. Gribble, J. Nat. Prod., 49, 449 (1986).
9. mp 122-125°C; IR (KBr) λ 3420(br), 1695, 1615-1605 cm^{-1}; NMR($CDCl_3$) δ 9.16(1H, s), 8.59(1H, d, J=5.2), 8.41-8.37(1H, m), 7.65(1H, d, J=5.2, H), 7.52-7.50(1H, m), 7.27(1H, d, J=2.6, H), 7.19-6.90(1H, m), 6.84(1H, s), 1.74(3H, s, CH_3); MS, 265 (M+1).

10. mp 170-172°C; IR(KBr) λ 3380, 1770, 1650, 1620, 1455, 1385 cm^{-1}; NMR($CDCl_3$) δ 9.01(1H, s), 8.90(1H, br, s), 8.77(1H, d, J=5.0), 7.39(1H, d), 7.25(1H, d), 7.15(1H, t), 7.105(1H, t), 6.50(1H, s), 2.05(3H, s, CH_3); MS, 266 (M+1).
11. mp 143-145°C; IR(KBr) λ 2975, 2960, 1680, 1590, 1450, 1420, 1375, 1330, 1245, 1160, 1100, 1090, 1005, 960, 850, 750 cm^{-1}; NMR($CDCl_3$) δ 9.53(1H, s), 8.88(1H, d, J=5.2), 8.65(1H, d, J=8.0), 7.68(1H, d, J=5.2), 7.62-7.58(1H, m), 7.46-7.33(2H, m), 6.84(1H, s, indole-H_3), 1.85(3H, s, CH_3), 1.57(s, H_2O), -0.18(9H, s, $Si(CH_3)_3$); MS, 337 (M+1).
12. Part NMR($CDCl_3$) δ 6.05(1H, s, indole-H_3), 2.03(3H, s, CH_3), 1.67(3H, s, CH_3), 1.63(3H, s, CH_3); MS, 296 (M^+).
13. The experimental details will be published in a forthcoming paper.
14. F. A. Carey; A. S. Court, J. Org. Chem., 37, 1926 (1972).
15. (a) J. E. Richman; J. L. Herrmann; R. H. Schlessinger, Tet. Lett., 35, 3267 (1973); (b) J. L. Herrmann; J. E. Richman; R. H. Schlessinger, Tet. Lett., 35, 3271 (1973); (c) J. L. Herrmann; J. E. Richman; R. H. Schlessinger, Tet. Lett., 35, 3275 (1973).
16. M. Nakane, C. R. Hutchinson, J. Org. Chem., 43, 3922 (1978).
17. mp 256-258°C (dec.); IR(KBr) λ 3140, 2940, 1615, 1595, 1460, 1410, 1370, 1320, 1260, 1245, 1145 cm^{-1}; NMR($CDCl_3$) δ 10.51(1H, s, H_1),8.51(1H, d), 8.32(1H, t), 7.83(1H, d, J=6.2, H), 7.52-7.47(2H, m), 7.33-7.27(2H, m), 6.68(1H, s, $(CHSEt)_2$), 2.77(3H, s, CH_3), 2.72-2.64(4H, q. $(CH_2CH_3)_2$), 1.24-1.16(6H, t. $(CH_2CH_3)_2$); MS, 367 (M+1).
18. E. J. Corey; D. J. Beames, J. Am. Chem. Soc., 95, 5829 (1973).
19. J. English, Jr.; P. H. Griswold, Jr., J. Am Chem. Soc., 67, 2040 (1945).
20. D. W. Graham; W. T. Ashton; L. Barash; J. E. Brown; R. D. Brown; L. F. Canning; A. Chen; J. P. Springer; E. F. Rogers, J. Med. Chem., 30, 1074, (1987).
21. A. J. Ratcliffe, M. Sainsbury, A. D. Smith, J. Chem. Soc. Perkin Trans. I, 2933 (1988).
22. C. A. Reece; J. O. Rodin; R. G. Brownlee; W. G. Duncan; R. M. Silverstein, Tet., 24, 4249 (1968).
23. G. Stork; K. Zhao, Tet. Lett., 30, 287 (1989).
24. When methanol was used instead of acetonitrile, a mixture of acetal **15** and aldehyde **7** was obtained which were taken up in acetonitrile and then stirred with 20% aqueous HCl for 30 min at room temperature. The aldehyde in its HCl salt form was collected as a red precipitate .
25. mp 320-330°C (dec); IR(KBr) λ 1675, 1640, 1600, 1420, 1245, 1065, 1020, 810, 745 cm^{-1}; NMR(DMSO-d_6) δ 11.53(1H, s H_1), 10.36(1H, s, CHO), 8.63(1H, d, J=8.0 Hz, H_{10}), 8.54(1H, d, J=5.8, H_3), 8.06(1H, d, J=5.8, H_4), 7.62(2H, m, H_7, H_9), 7.26(1H, m, H_8), 3.67(s, H_2O), 2.91(3H, s, CH_3); MS, 261 (M+1).
26. mp 312-320°C (dec.); IR(KBr) λ 3240, 3050, 2900, 2870, 1600, 1465, 1410, 1245, 1035, 995, 810, 740 cm^{-1}; NMR(DMSO-d_6) δ 11.50(1H, s, NH), 9.78(1H, s, H_1), 8.42(2H, d, J=6.4, H_3, H_{10}), 7.94(1H, d, J=6.0, H_4), 7.59-7.52(2H, m, H_7, H_9), 7.29-7.21(1H, t, H_8), 5.58(3H, br, s, CH_2OH), 2.82(3H, s, CH_3); MS, 263 (M+1).
27. All new compounds gave satisfactory analyses. **12** was not submitted for analysis.

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