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# SYNTHESIS OF ELLIPTICINE

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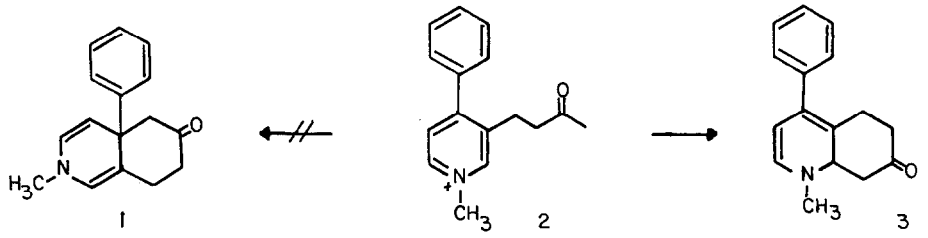
Abstract. The 6H-pyrido[4,3-b]carbazole system is efficiently synthesized by intramolecular attack of an ester enolate on an unactivated pyridinium salt.

During the course of studies of the intramolecular addition of enolates to unactivated pyridinium ions we sought to determine the regioselectivity of addition vis a vis reaction at C-2 or C-4 of the pyridinium salt[1]. The intermolecular attack of enolates is well documented to occur at C-4 of the pyridinium species[2]. An earlier attempt to exploit this apparent regioselectivity for the synthesis of the 4a-phenyldecahydroisoquinoline system by intramolecular addition was unsuccessful[1a]. In that example, salt 2 was not converted into the desired 1, but instead gave the 4-phenylquinoline derivative 3. Here, however, the 1,2 adduct is favored by both steric and resonance factors. In order to perform a more unbiased test of the regioselectivity of the reaction, we attempted the synthesis of the 6H-pyrido[4,3-b]carbazole system of ellipticine 5, an antitumor, antileukemic agent[3] isolated from several plants of the family *Apocyanaceae*[4].

The general route to ellipticine is shown below. A previous report of this bond construction sequence was presented by Bergman who pyrolyzed 4a to give ellipticine 5[5]. Unfortunately 10% of the product was the unwanted isomeric 10H-pyrido[2,3-b]carbazole 6. In our system, the relative amounts of these products would be determined by the relative amounts of 1,2 and 1,4 addition from 4b. While our work was in progress, Pandit published a closely related synthesis of ellipticine analogs using the more usual addition to an activated pyridinium species (4c) which incorporated an electron withdrawing substituent at the pyridinium C-3[2h,i]. Significantly, only the N-6 methyl derivatives have been prepared thus far. As shown below, the route via the unactivated salt 4b allows rapid construction of the N-6 unsubstituted ellipticines.



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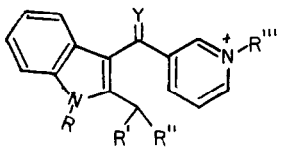
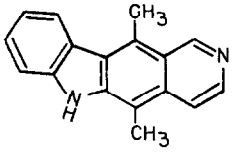
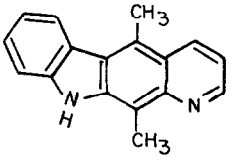






4a R=R'=H, R''=$CH_3$, R'''=Bu, Y=$CH_2$

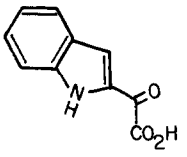
4b R=R'=H, R''=$CO_2CH_3$, R'''=$CH_3$, Y=$CH_2$

4c R=R'=$CH_3$, R''=$CO_2Et$, R'''=$CH_2Ph$, Y=O

5 6

The oxoacid 7 was converted into ester 8b in 81% yield by Wolff-Kishner reduction and methylation[6-9]. Condensation of 8b with 3-acetylpyridine in $HBr/CH_3OH$ gave the indolyl pyridyl ethene 9a[10] (mp 160 - 161°C) in 82% yield[5a]. Methylation to 4b and immediate treatment with $NaOCH_3/CH_3OH$ produced the dihydroellipticine derivative 10[10] in 62% yield, presumably by isomerization of the expected dihydropyridine. The unstable 10 was more conveniently converted directly to the fully aromatic species 12a[10] (mp 317 - 321°C, d) by addition of nicotinate 11 to the reaction mixture. In this manner, 12a crystallized directly from the reaction in 78% overall yield from 9a. $^1H$ NMR shows no contamination of 12a by isomeric materials.

Since it was not possible to examine the first formed dihydropyridine in the conversion of 4b to 10, 9a was reduced to the indolyl pyridyl ethane 9b[10] (mp 119 - 119.5°C) ($H_2$,Pd/C,$CH_3OH$), then methylated and treated with $NaOCH_3/CH_3OH$ to give 13[10] as a mixture of stereoisomers in 84% yield. Upon treatment with excess 11, 13 also gave 12a (57% from 9b). Analysis of 13 by 360 MHz $^1H$ NMR revealed three major stereoisomers (> 90% of the total) as indicated by the C-11 methyl doublets at $\delta$ = 1.42, 1.44, 1.58 (12/67/21 relative areas). The assignment of these isomers as 1,4 adducts rested upon the presence of three singlets due to H-1 at $\delta$ = 5.88, 5.90, 5.98 (13/68/18 relative areas). Also present in this region were the expected doublets for H-3 ($\delta$ = 5.83, 5.88)[11]. Although small amounts



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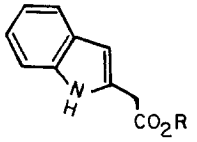
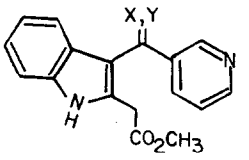


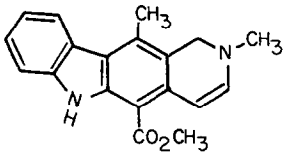
8a R=H

8b R=$CH_3$



9a X,Y = $CH_2$

9b X=H,Y=$CH_3$



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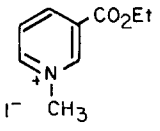

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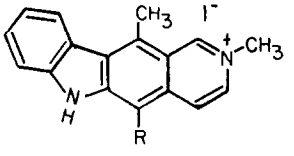
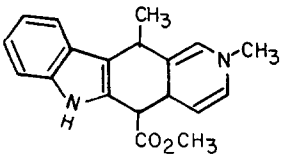


12a R=$CO_2CH_3$

12b R=$CH_3$



13

of other stereoisomers were present clearly the 1,4 adducts greatly predominated. In an attempt to determine if the products derived from kinetic or equilibrium control, 13 was subjected to conditions known to allow reversible formation of ester enolate/dihydropyridine adducts[1a]. Unfortunately, the adducts rapidly decomposed. We are further exploring this question and also pursuing the possibility of achieving 1,2 addition.

Conversion of 12a to ellipticine was easily accomplished. Reduction with Vitride® in xylene at 130°C and immediate oxidation of the product with methanolic 11 gave the known salt 12b in 85% yield[12,13]. An interesting feature of this sequence is the direct preparation of the 2-methyl-6H-pyrido[4,3-b]carbazolium salts, themselves potent antitumor agents[14]. Demethylation of 12b with sodium thiophenoxide/DMSO gave a 91% yield of ellipticine 5[12], which was spectrally and chromatographically identical to an authentic sample.

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7. Acid 7 was treated with ethanolic hydrazine and KOH at 80°C for 1 hr then at 150°C until $N_2$ evolution was complete. Workup gave 8a[8] and esterification with $CH_2N_2$ gave 8b.[9]

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