Chemistry of 6*H*-Pyrido[4,3-*b*]carbazoles

Part 10†—Carbon-13 Nuclear Magnetic Resonance Spectra of Ellipticines and some Model Compounds

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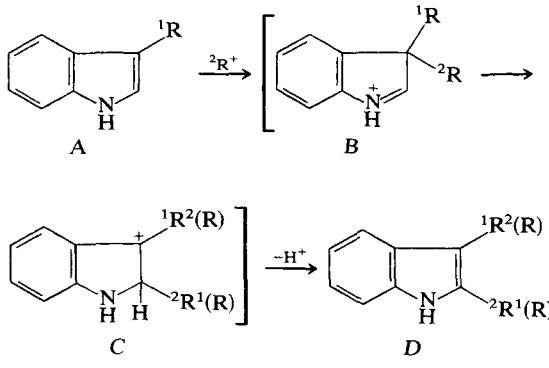
The ^{13}C NMR spectrum of ellipticine has been re-interpreted by reference to model compounds, and correlated with the spectra of a number of new ellipticine derivatives.

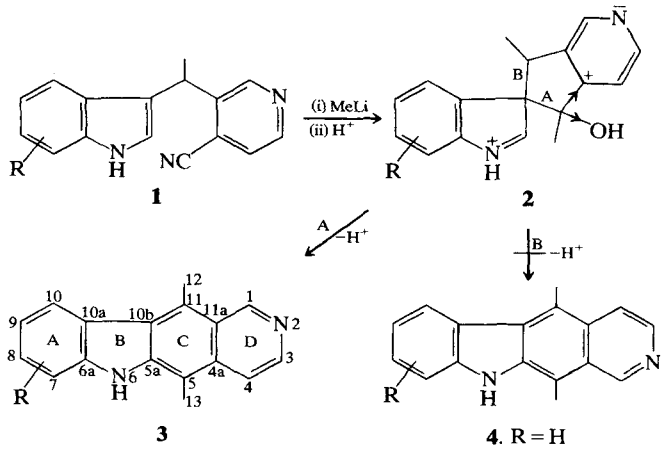
INTRODUCTION

It is well known[2] that electrophilic attack upon a 3-substituted indole *A* frequently leads first to a 3,3-disubstituted intermediate *B* which re-arranges to a cation *C* and, thence, by deprotonation, to a 2,3-disubstituted indole *D*. Which of the two substituents migrates in this sequence depends upon the strengths of the bonds concerned and the relative stabilities of the two possible cations *C*. Of course, a direct attack upon the α-position of the indolyl unit is also possible.



In our synthesis of 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines)[3] the nitrile **1**, R = H, when treated with methyllithium and worked up in the presence of acid, affords ellipticine (**3**, R = H) rather than isoellipticine (**4**). Should a spiro intermediate, **2**, R = H be involved in the regiospecific formation of the tetracyclic system, **3**, R = H, then the selective breaking of bond A probably depends upon inductive effects due (i) to the electron deficiency of the pyridine 4-position and (ii) to the α-oxygen atom (these effects, which show specific electron withdrawal from bond A, are summarized in formula **2**).

Since ellipticines are important anticancer agents,[4] there is an increasing interest in the preparation of derivatives substituted in the benzenoid ring. In our synthesis, the electronic properties of additional substituents may well change the balance which determines the direction of ring closure and it is thus, vital



that the required tetracyclic system is readily recognized. One technique which might be used for this purpose is ^{13}C NMR, but it was surprising to find that the two sets of published data for ellipticine (Table 1) do not entirely correspond, either in chemical shift positions or in the assignments to given carbon atoms, particularly those of C-1, C-4a, C-5, C-5a, C-6a, C-10a, C-10b and C-11a.

In view of these discrepancies we have re-examined the ^{13}C NMR of ellipticine, and extended the study to include a number of new derivatives made by the cyclization of nitriles of type **1**.[1]

RESULTS AND DISCUSSION

Prior to a re-examination of the ^{13}C NMR spectra of ellipticine and some of its derivatives, we have analysed in detail the spectra of a number of intermediates of known structures[1] and assigned the observed resonances by reference to simpler model compounds. For example, chemical shift assignments taken from the literature for indole (**5**),[7] 5-methoxyindole (**6**),[8] carbazole (**7**),[7] pyridine (**8**)[8] and isoquinoline (**9**)[8] are not in dispute, and are shown here alongside the atom to which they refer. Similarly represented are the data which we have compiled for 1,4-dimethylcarbazole (**10**), 6-methoxy-1,4-dimethylcarbazole (**11**), 3-ethylpyridine (**12**) and 3-acetylpyridine (**13**).

† For Part 9, see Ref. 1.
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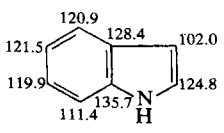
Table 1. Literature ^{13}C data for ellipticine

Carbon atom	Chemical shift assignments																
	1	3	4	4a	5	5a	6a	7	8	9	10	10a	10b	11	11a	12	13
Ref. 5	149.5	140.4	115.7	140.9	123.0	142.6	132.4	110.6	127.0	119.1	123.7	127.9	107.9	123.3	121.9	14.2	11.8
Ref. 6	152.9	140.9	115.8	132.3	107.9	140.4	142.6	110.5	127.0	119.1	123.6	123.3	121.9	123.0	123.3	14.2	11.8



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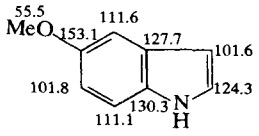

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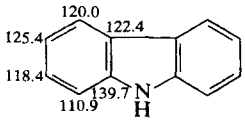

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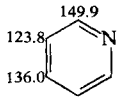

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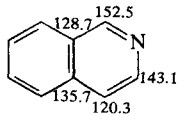

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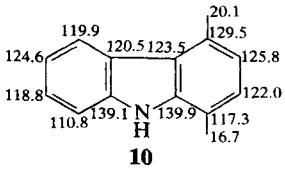

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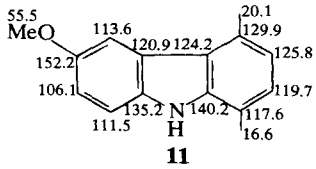

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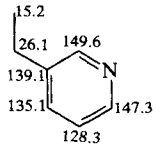

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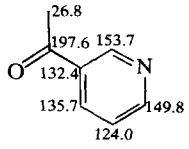

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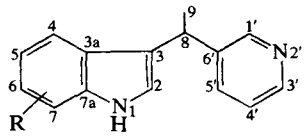
With the aid of these models it is now possible to correlate the resonances for the indolylpyridylethane precursors (**14**)[9] of ellipticine; in particular, an analysis of the multiplicities and the coupling constants in the fluorine derivative (**14**, R = 7-F) leads to unequivocal proof of the assignments in the benzenoid ring *ortho*, *meta* and *para* to the site of substitution by the fluorine atom [J(F, 7) = 244 Hz, J(F, 6) = 21 Hz, J(F, 7a) = ~18 Hz, J(F, 5) = 8 Hz, J(F, 3a) = ~8 Hz, J(F, 4) = 35 Hz].

For simple aromatic systems, the substitution of an H by a Cl atom brings about a downfield shift of ~6 ppm in the position of the carbon resonance involved. However, a comparison of the spectra of the parent indolylpyridylethane and its 7-chloro derivative (**14**, 1st and 3rd entries in Table 2) shows a chemical shift change of 16.7 ppm in the C-7 resonance. The origin of this effect is unknown, but it may reflect a situation peculiar to the indole system; a similar discrepancy, though not so large, is noted in the spectra of the corresponding ellipticines (Table 3).



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In support of these conclusions, the ^{13}C assignments for the nitrile **15**, for the alcohol **16** and for the ketone **17** are summarized alongside the formulae.

From these results we are now able to re-analyse the ^{13}C NMR spectrum of ellipticine but, interestingly, our set of chemical shifts (entry 2, Table 3) are slightly different to either of the two previous compilations (Table 1). In order to be certain that an authentic

Table 2. ^{13}C NMR Assignments for indolylpyridylethanes 14

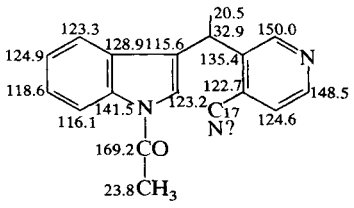
R	2	3	3a	4	5	6	7	7a	8	9	1'	3'	4'	5'	6'	Me	MeO
H	126.2	118.3[a]	123.2[a]	121.0	121.8	118.6	111.4	141.5[a]	33.9	21.9	148.8	147.0	121.0	136.7	131.4[a]	—	—
7-Me	123.2	119.0[a]	121.5	118.5	121.5	116.3	125.9[a]	142.4[a]	33.9	21.9	148.8	147.0	121.5	134.4	136.1[a]	16.6	—
7-Cl	123.3	119.9[a]	115.9[a]	119.3	120.5	117.7	128.1[a]	141.9[a]	33.7	21.7	148.7	147.0	120.5	134.4	133.3[a]	—	—
7-F	123.2	119.7[a]	123.2	114.9[b]	118.6[b]	105.8[b]	148.0[a]	132.1	33.8	21.8	148.8	147.1	123.2	134.4	130.5[a]	—	—
5-OMe	123.2	118.4[a]	126.7[a]	112.1	153.0[a]	101.2[7]	111.0	142.3[a]	33.9	21.8	148.9	147.0	122.7	134.5	132.0[a]	—	55.4

[a] Singlet.
[b] Double doublet (secondary coupling to fluorine), all other peaks appear as doublets in the off resonance decoupled mode.

Table 3. ^{13}C NMR Assignments for ellipticines 3[a]

	R	1	3	4	4a	5	5a	6a	7	8	9	10	10a	10b	11	11a	12	13	Me	MeO
1	H	153	143	120	136	120	140	139	111	119	125	120	121	124	130	129	20	17	—	—
2	H[e]	149.7	140.5	123.7	132.5[c]	107.9[c]	142.7[c]	140.4[c]	110.7	115.8	127.1	123.4	121.9[c]	123.1[c]	127.8[c]	126.9[c]	14.3	11.9	—	—
3	H[b]	143.7	142.5	123.6	133.3[c]	113.3[c]	142.2[c]	142.3[c]	111.2	118.9	127.1	119.2	120.2[c]	123.9[c]	128.1[c]	125.1[c]	14.5	11.7		
4	9-OMe[a]	149.6	140.3	123.6	132.4[c]	111.1[c]	141.3[c]	137.4[c]	107.8	108.0	153.2	115.1	121.7[c]	123.4[c]	128.1[c]	126.2[c]	14.1	11.6	—	55.9
5	7-Me[b]	144.2	143.1	119.4	129.4[c]	110.5[c]	141.5[c]	132.7[c]	126.0[c]	120.8	121.8	121.1	119.8[c]	121.9[c]	127.3[c]	133.8[c]	14.7	12.1	17.3	—
6	7-Cl[b]	143.7	143.7	122.5	134.6[c]	111.4[c]	141.1[c]	138.9[c]	121.5[c]	115.7	124.0	119.7	120.5[c]	124.0[c]	127.9[c]	133.4[c]	14.7	12.1	—	—
7	7-F[b]	144.1	143.9	121.0	134.0[c]	111.0[c]	142.7[c]	130.3	149.4[c]	113.8[d]	125.6[d]	119.6[d]	120.9	121.0[c]	127.9[c]	133.3[c]	14.6	11.8	—	—

[a] DMSO-d_6.
[b] 10 % TFA added.
[c] Singlet.
[d] Double doublets.
[e] J(F, 1) = 240 Hz, J(F, 8) = 18 Hz, J(F, 6a) = ~15 Hz, J(F, 9) = J(F, 10a) = 7 Hz, J(F, 10) = 2.5 Hz.



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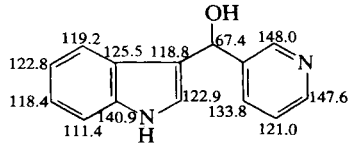

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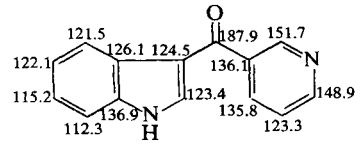

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sample of ellipticine was being studied, our sample was compared with the natural product[10] and also with a synthetic specimen prepared by Swedish colleagues.[11] The three samples are identical in every respect (TLC, mixed m.p., UV, IR, ^{1}H and ^{13}C NMR) and it was noted that the ^{13}C NMR spectra are not concentration dependent. When our chemical shift data are compared with those of earlier workers, differences are noted in the positions of the low field resonances associated with the pyridine ring, and the absence of a peak at δ119.1. Instead, we observe a singlet at δ126.9.

Entry 1 in Table 3 shows the projected ^{13}C resonance positions of ellipticine in DMSO-d_6, deduced from the combined spectra of 1,4-dimethylcarbazole and isoquinoline. Unfortunately the 7-substituted ellipticines are not very soluble in DMSO-d_6, and their spectra (entries 5, 6 and 7) were recorded in DMSO-d_6 containing 10% trifluoroacetic acid. Thus, for comparison purposes, entry 3 refers to the spectrum of ellipticine rerun in this solvent mixture. The interpretation of the spectrum of 9-methoxyellipticine (entry 4) is simplified by the preliminary analysis of the ^{13}C NMR data for 6-methoxy-1,4-dimethylcarbazole (**11**), and in the case of 7-fluoroellipticine (entry 7) an examination of CF coupling constants and the multiplicity of the signals involved allows an absolute assignment of resonances within ring A.

It is unfortunate that at the present time samples of isoellipticines are not available, so that direct ^{13}C NMR comparisons with ellipticines cannot be made. However, the correlation between the known compounds, ellipticine and 9-methoxyellipticine, with the new derivatives described here is sufficiently good that we are certain they are also 6*H*-pyrido[4,3-*b*]carbazoles. This conclusion is backed by a wealth of other chemical and physical data.[1]

EXPERIMENTAL

Natural abundance ^{13}C spectra were obtained in the pulsed Fourier transform mode at 22.50 MHz using a JEOL FX 90Q spectrometer. Unless stated otherwise, the samples were dissolved in perdeuterodimethyl sulphoxide and recorded at a concentration of 20–40%. Chemical shifts were measured in ppm downfield from TMS as internal standard. Each spectrum was recorded in the broad band decoupled mode, as well as under appropriate off-resonance conditions.

Each compound described in this paper has been fully characterized and details of this work are to be found in Refs 1, 3 and 9.

Acknowledgements

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