235. A 300 MHz NMR. Evidence for the Configuration of Roxburghine B

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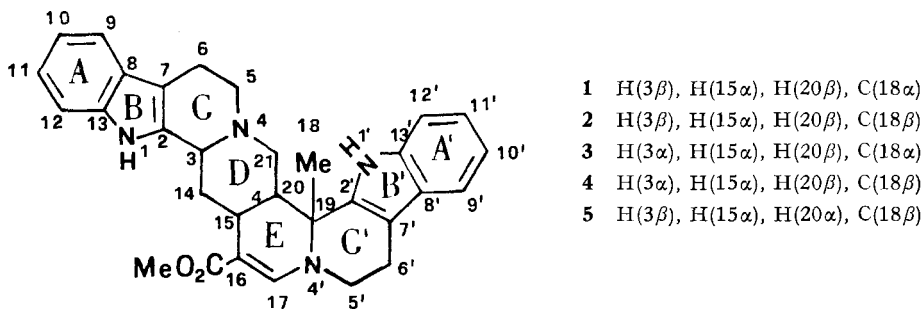Istituto di Chimica, Politecnico di Milano, 20133 Milano, Italy[2])

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Summary. The 300 MHz ^{1}H-NMR. spectrum of the alkaloid Roxburghine B is completely analysed. The coupling constant values give evidence for the configuration, which is revised to *epi-allo*: H(3β), H(15α), H(20α) and C(18β).

The Roxburghines D, E, C and B are indole alkaloids which have been isolated [1] from a species of *Uncaria* (most probably *Uncaria elliptica*) [2]. Their structure and configuration were established as **1–4** on the basis of ^{1}H–NMR. evidence and of some chemical interconversions [1] [3]. Total synthesis of Roxburghine D (**1**) has also been accomplished [4].

1	H(3β), H(15α), H(20β), C(18α)
2	H(3β), H(15α), H(20β), C(18β)
3	H(3α), H(15α), H(20β), C(18α)
4	H(3α), H(15α), H(20β), C(18β)
5	H(3β), H(15α), H(20α), C(18β)

In particular, the NMR. data obtained from the 100 MHz ^{1}H–NMR. spectrum of Roxburghine B were not sufficient for the assignment of the configuration. Therefore the *normal* ajmalicinoid configuration (**4**) was deduced from Zn/acid conversion of Roxburghine E to Roxburghine B, on the assumption that this reaction involved the epimerization at C(3) only [5].

As the ^{13}C–NMR. data for Roxburghines [6] did not appear consistent with the *normal* configuration for Roxburghine B, suggesting on the contrary an *epi–allo*

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configuration, the ¹H–NMR. study at 300 MHz was undertaken. These analyses confirm the *epi–allo* configuration (**5**) for Roxburghine B and give evidence for the preferred conformation (**5a**). The revised configuration requires a different interpretation of the mechanism of the isomerization. A proposal for this mechanism is given in the accompanying paper [6].

Results. – The spectrum of Roxburghine B is reported in the Figure. INDOR technique was extensively used instead of spin-decoupling in order to detect hidden signals and to measure the coupling constants whose values are necessary for the determination of the configuration. Actually many signals still overlapped or were disturbed by some impurities which could not be eliminated or shifted by changing solvent. This holds in particular for the key protons of the piperidine ring D at C(3), C(14), C(15) and C(20)

Only one INDOR experiment is reported in the Figure: by monitoring line 1 to 6 of the signal at 3.75 δ (H$_{ax}$–C(5′))³) the connected lines at 3.61, 2.86 and 2.71 δ (H$_{eq}$–
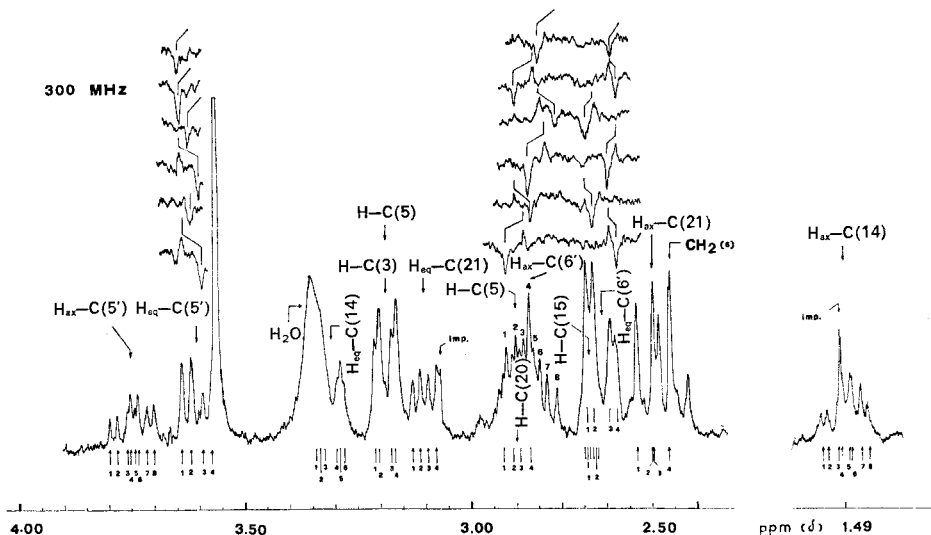
300 MHz ¹H-NMR. spectrum (acetone-d₆) *of Roxburghine B* (**5**). In the insert from the top, INDOR spectra by monitoring line 1 to 6 of the signal at 3.75 δ

C(5′), H$_{ax}$–C(6′) and H$_{eq}$–C(6′)) were perturbed, as shown in Table 1. These results, also confirmed by monitoring some lines of H$_{eq}$–C(5′), give all the coupling constants values including their signs (Table 2), and allow the identification of the coupled protons.

The presence of two geminal interactions evidences the fragment indolyl-CH₂–CH₂–N$<$, which may belong to ring C or C′. The protons of the other similar fragment

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³)   The terms equatorial and axial will be used throughout the paper as pseudo-equatorial and pseudo-axial for the sake of brevity.

Table 1. *Analyses of INDOR spectra*[a])

Monitored H_{ax}—C(5′)	H_{eq}—C(5′)	Perturbed H_{ax}—C(6′)	lines H_{eq}—C(6′)
[b]) 1	[c]) 1 r –	[b]) 6 r –	[c]) 3 r –
2	1 r –	2 r, 5 p	3 p, 4 r
3	2 r –	6 p, 8 r	1 r, 2 p
4	1 p, 3 r	4 r, 7 p	3 r, 4 p
5	2 r –	– 5 r	1 p, 2 r
6	1 p, 3 r	1 r, 3 p	3 p, 4 r
H_{ax}—C(14)	H_{eq}—C(14)	H—C(3)	H—C(15)
[b]) 1	[c]) 1 r, 4 p	1(2) r, 4 p	[c]) 1 r, 2 p
2	2 r, 5 p	1(2) r, 4 p	1 p, 2 r
4	1 p, 4 r	1(2) r –	1 r, 2 p
5	3 r, 6 p	2 p, 4 r	1 p, 2 r
7	2 p, 5 r	1(2) r, 3(4) p	1 r –
8	3 p, 6 r	1(2) r, 3(4) p	–
H_{eq}—C(21)	H_{ax}—C(21)	H—C(20)	
[b]) 1	[b]) 1 r, 2(3) p	[c]) 3 r, 4 p	
2	2(3) r, 4 p	3 p, 4 r	
3	1 p, 2(3) r	1 r, 2 p	
4	2(3) p, 4 r	1 p, 2 r	
H_{ax}—C(21)	H_{eq}—C(21)	H—C(20)	
[b]) 1	[c]) 1 r, 3 p		
2	2 r, 4 p		
3	1 p, 3 r	–	
4	2 p, 4 r		

[a])   r is for regressive and p for progressive lines; lack of data means that the INDOR signals were not detectable or not analysed.
[b])   Single lines.
[c])   Degenerate lines.

Table 2. *^1H-NMR. Parameters for Roxburghine B* (5)

TMS	Acetone	BPA[a])	J (Hz)			
H—C(3)	3.19	3.73	$J_{14ax,14eq}$	– 13.0	$J_{5′ax,5′eq}$	– 13.5
H_{ax}—C(14)	1.49	1.66	$J_{3,14ax}$	11.5	$J_{6′ax,6′eq}$	– 15.0
H_{eq}—C(14)	3.31	3.47	$J_{3,14eq}$	2.5	$J_{5′ax,6′ax}$	11.0
H—C(15)	2.74	∼3	$J_{14ax,15}$	3.8	$J_{5′ax,6′eq}$	5.0
H—C(20)	2.90	∼3	$J_{14eq,15}$	2.5	$J_{5′eq,6′ax}$	6.5
H_{eq}—C(21)	3.10	3.17	$J_{21ax,21eq}$	– 10.5	$J_{5′eq,6′eq}$	⩽ 1
H_{ax}—C(21)	2.60	2.67	$J_{20,21eq}$	5.0	$J_{5′eq,17}$	≤ 1
H_{ax}—C(5′)	3.75	3.58	$J_{20,21ax}$	11.0		
H_{eq}—C(5′)	3.61	3.37	$J_{15,20}$	≤ 2		
H_{ax}—C(6′)	2.86	2.82	$J_{15,17}$	2.0		
H_{eq}—C(6′)	2.71	2.62				
H—C(17)	7.42	–				

[a])   Benzene/pyridine/acetone 30 : 65 : 5 (v/v).

were identified at 2.55 δ (2H–C(6)), 2.9 and 3.2 δ (2H–C(5)), but their analysis was unsuccessful, since the spin system is strongly coupled (2nd order). As the spectrum in benzene/pyridine/acetone shows a response of the proton at 3.37 δ by monitoring H–C(17) (see Table 2), a small long range coupling occurs between H–C(17) and H_{eq}–C(5') (see also Roxburghine D [1]), thus supporting the assignment of the fragments to ring C and C'. That the ring C' exists in a preferred conformation is shown by the non-averaging of the coupling constants values. In particular the nearly zero value of $J_{5'eq,6'eq}$ ($\vartheta \sim 90°$) suggests a distortion of ring C' from the half-chair conformation. This could also be due to the conjugation of the enamino nitrogen atom N(4') with the α,β-unsaturated ester group.

The remaining protons of the high field portion of the spectrum belong (except for the methyl groups) to the piperidine ring D. Monitoring H–C(17) lines, the position of H–C(15) (overlapped by H_{eq}–C(6')) was detected at 2.74 δ; the fine structure was not resolved as a result of the complex pattern of H–C(15) but the INDOR spectra are clear enough to exclude any diaxial coupling ($J \sim 10$ Hz) for this proton. Monitoring six of the eight lines of H_{ax}–C(14) responses appeared at 3.31, 3.19 and 2.74 δ and the analysis of the INDOR spectra led to the coupling constants values reported in Table 2. The negative sign of $J = 13.0$ Hz allows the assignment of the geminal protons at C(14) and their connections with H–C(3) and H–C(15). The relationship of H–C(15) with H–C(20) and 2H–C(21) was completed by monitoring the four lines at 2.6 δ (H_{ax}–C(21) partially overlapped by 2H–C(6)). The absorptions of H_{ax}–C(21) could be selected and the hidden pattern of H–C(20) appeared: two couplings of resp. 11.0 and 6.0 Hz were evidenced, while the smallest one ($J_{15,20}$), less than 2 Hz, is not resolved. The results of Table 1 show that the interaction involving the geminated nuclei at 3.10 and 2.60 δ is negative, thus confirming the assignments reported.

Discussion. – A *trans* C(15)/C(20) ring-junction for Roxburghine B is excluded (in contrast with the other isomeric Roxburghines) by the values of $J_{15,20}$, $J_{15,14ax}$ and $J_{20,21ax}$. Moreover these values indicate that H–C(15) must be equatorial and H–C(20) axial. It means that an inversion of configuration occurs at C–(20), but not at C(3), during the conversion of Roxburghine E into Roxburghine B. In fact the three possible conformations with H(3α) configuration require a *trans* or *cis* C(3)/N(4) junction with H–C(15) axial and H–C(20) equatorial, or a *cis* junction with H–C(3) equatorial, which are all ruled out by the experimental results.

The β orientation for the angular methyl group has been established previously [1] by chemical correlation.

The three energetically preferred conformations for structure (5) are (5a, 5b and 5c). The conformation 5c is immediately ruled out by the orientations of H–C(3) and H–C(20) (equatorial) and H–C(15) (axial) which are not consistent with the coupling constants values. For 5b, the *cis* relationship between H–C(3) and the nitrogen lone pair does not explain the upfield shift for the proton (3.19 *vs.* 4.31 and 4.45 δ for Roxburghine D and E [3]). Thus Roxburghine B exists preferentially in the conformation 5a. The same conclusions have been reached from the analysis of 13C–NMR. spectra [6].

5 a

inv. N(4)

inv. ring D

5 c

5 b
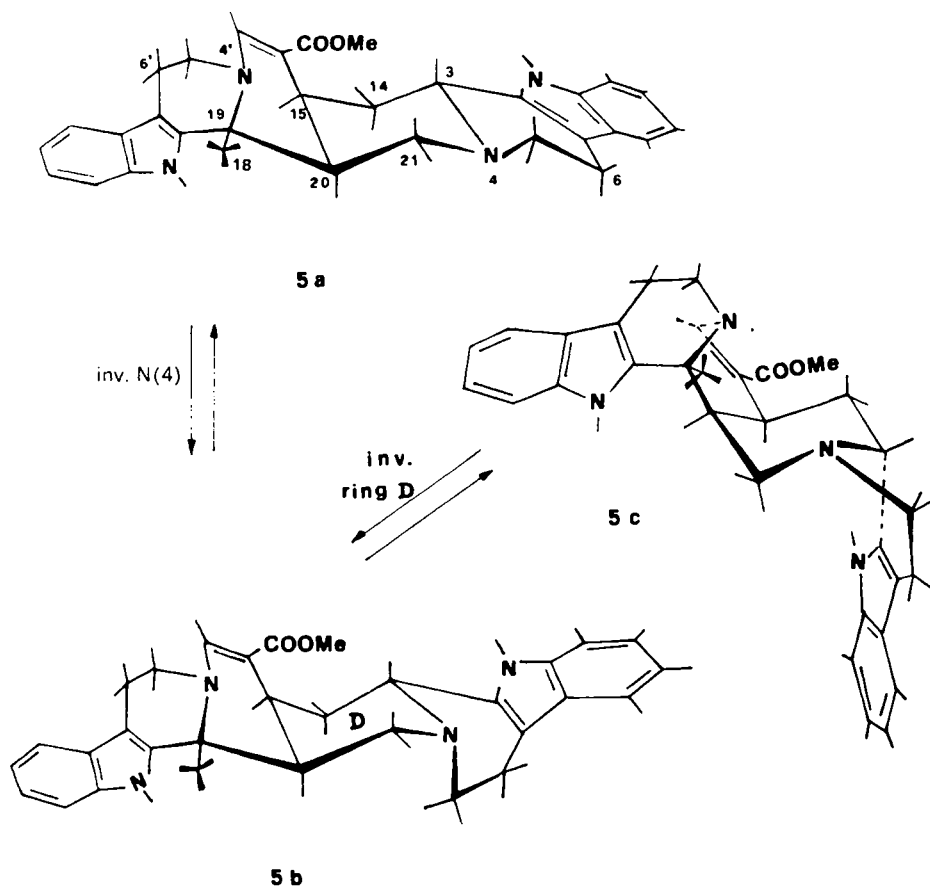
Experimental Part. – NMR. spectra of Roxburghine B were measured at 300 MHz with a *Varian* HR-300 spectrometer. INDOR experiments were performed with a Sc 8525-2 unit. Chemical shifts are in ppm (δ) from TMS as internal standard. Two solvents were used, acetone-d_6 and acetone/benzene/pyridine 5:30:65 (v/v) in order to avoid at most the overlapping of the signals. Concentrations were *ca.* 20 mg/ml. Samples were degassed prior to double irradiation experiments by freezing and pumping.

REFERENCES

[1] L. Merlini, R. Mondelli, G. Nasini & M. Hesse, Tetrahedron 26, 2259 (1970).

[2] J. D. Phillipson & S. R. Hemingway, J. Pharm. Pharmac. 25, Suppl., 143P (1973) and J. Chromat. 105, 163 (1975).

[3] C. Cistaro, L. Merlini, R. Mondelli & G. Nasini, Gazz. chim. Ital. 103, 153 (1973).

[4] G. Benz, H. Riesner & E. Winterfeldt, Chem. Ber. 108, 248 (1975).

[5] A. J. Gaskell & G. A. Joule, Tetrahedron 24, 5115 (1968).

[6] L. Merlini, R. Mondelli, G. Nasini, F. W. Wehrli, E. W. Hagaman & E. Wenkert, Helv. 59, 2254 (1976).