236. ^{13}C-NMR. Analysis of the Roxburghines[1])

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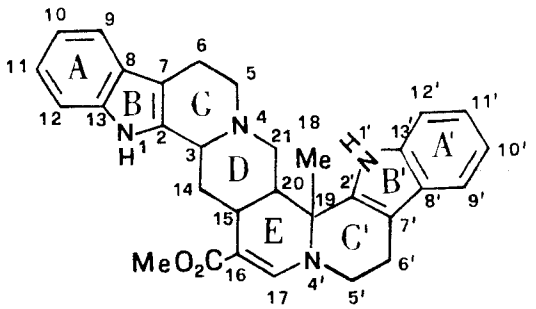
Summary. The ^{13}C shifts of the alkaloids roxburghine B, C, D and E are determined. They confirm the following configurations for the last three bases: C(18α)-*normal*, C(18α)-*pseudo* and C(18β)-*pseudo*, respectively. Roxburghine B is shown to be a C(18β)-*epi-allo* isomer.

Introduction. – A Malaysian species of *Uncaria*[4]) produces a variety of indole alkaloids including a group of $C_{31}H_{32}N_4O_2$ isomers, named the roxburghines [3]. Their structure determination showed the isomers D,E,C and B to be represented by formulae **1**, **2**, **3** and **4** [3] [4]. Since these compounds are tryptaminyl ajmalicinoid substances and since an exhaustive ^{13}C-NMR. analysis of indole alkaloids of the ajmalicine type has been completed recently [5], it was of interest to inspect the roxburghines by this powerful tool of structure analysis. The present communication constitutes such a study.



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)

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[1]) ^{13}C-NMR. Spectroscopy of Naturally Occurring Substances. XLVI. For part XLV see [1].
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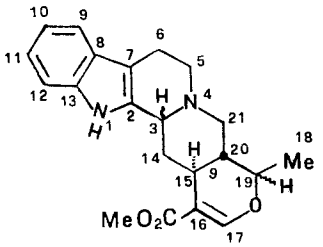
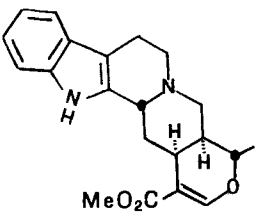
[4]) Most probably *Uncaria elliptica* [2].

Discussion. – The ^{13}C-shift assignment of the roxburghines (Table 1) is facilitated greatly by the earlier ^{13}C-NMR. analysis of ajmalicine(**6**), 3-iso-19-epi-ajmalicine(**7**), akuammigine(**8**), tetracyclic vinylogous amide **9** and by the data of tetrahydrocarbolines **10** and **11** (Table 2). The shifts of like carbon atoms in the two benzene rings of the roxburghines appear as separate signals but they cannot be identified on a one-to-one basis [5–7], while the C(7) shifts are distinguished from C(7′) by the perturbation of the latter by the angular methyl group. The assignment of C(2) *vs.* C(2′) in **1** and **2** is based on the expected upfield shift due to the change of C(3)/N(4) ring-junction. The non-aromatic carbon atoms are assigned on the basis of (i) the



6 H(3α), H(19β)
7 H(3β), H(19α)



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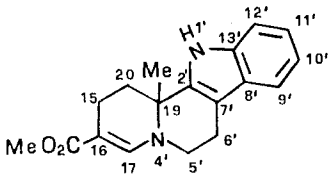

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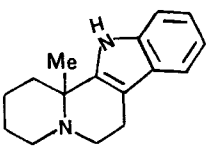

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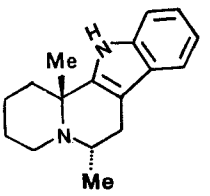

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electronegativity of substituents, (ii) the multiplicity of the signals and (iii) a chemical shift comparison with model compounds.

The roxburghines D (**1**) and E (**2**) have been shown to be *pseudo* ajmalicinoid compounds, differing only in the orientation of the angular methyl group [3] [4]. This is in full agreement with their ^{13}C-NMR. analysis. Both substances exhibit the C(3) and C(6) shifts of 54 and 17 ppm, respectively, characteristic of *pseudo* compounds [5]. As a consequence they also reveal nearly identical shifts of C(3), C(5), C(6), C(14) and C(2) with those of 3-iso-19-epi-ajmalicine(**7**). Despite the difference of the C(19) configuration of roxburghine D(**1**) and E(**2**), their C(21) center is under similar steric influence from C(18), C(2′) and N(1′) a condition which leads to like C(21) shifts.

The latter being close to C(21) shift of model **7** indicates that the shift perturbation of ring B′ acting on C(21) is nearly zero. The opposite configuration at C(19) with the consequent different orientation of the angular methyl for **1** and **2** (axial *vs.* equatorial to ring E) is shown by the deshielding of C(18) in **2**, *i.e.* the removal of γ-effects from C(15) and C(17). On the other hand, the quasi-axiality of the like methyl in the models **9** and **10** permits a comparison of the shift of this carbon atom for roxburghine D (**1**). The deshielding observed for these models (21–22 *vs.* 18 ppm) is in agreement with the

Table 1. *^{13}C chemical shifts of roxburghines*[a])

	1		**2**		**3**	**5**	
	acetone	$CDCl_3$	acetone	$CDCl_3$	acetone	acetone	$CDCl_3$
C(6)	17.6	17.1	17.5	17.0	(23.3)	(23.0)	(22.4)
Me(18)	18.1	18.7	26.9	26.6	18.7	26.6	26.0
C(6′)	23.0	22.6	23.0	22.3	(22.7)	(22.7)	(21.5)
C(15)	30.6	30.4	29.5	28.8	36.1	30.3	29.2
C(14)	32.9	32.4	32.8	31.9	35.3	32.0	30.8
C(21)	48.1	47.8	48.6	46.7	57.9	52.9	52.0
C(20)	49.4	50.6	49.3	48.4	50.0	42.7	41.7
OMe	49.4	50.4	50.8	50.7	50.1	50.8	50.7
C(5′)	49.9	49.4	47.4	47.7	50.7	46.6	46.2
C(5)	51.4	51.2	52.1	51.3	54.0	54.2	53.2
C(3)	54.0	54.2	55.1	54.2	60.6	56.0	55.1
C(19)	57.7	57.6	58.1	57.3	58.5	57.7	56.8
C(7′)	106.0	107.4	107.6	107.0	107.7	106.8	106.3
C(7)	108.1	110.2	109.7	109.2	109.9	108.1	107.6
C(12), C(12′)	110.2	111.4	112.2	111.6	111.7	111.8	110.8
	110.4	111.8	112.4	111.8	111.9	112.0	111.3
C(9), C(9′)	116.4	118.1	118.7	118.0	118.1	118.2	117.8
	117.0	118.7	118.8	118.0	118.8	118.5	117.8
C(10), C(10′)	117.5	119.5	119.8	119.7	119.2	119.3	119.0
	118.0	120.1	120.0	119.7	119.7	119.6	119.2
C(11), C(11′)	119.5	121.5	122.1	121.9	121.1	121.2	121.1
	120.4	122.5	122.4	122.2	122.2	121.9	121.6
C(8), C(8′)	125.5	126.7	127.7	126.9	127.3	128.2	127.1
	126.8	128.1	128.7	127.6	128.1	128.2	127.1
C(13), C(13′)	135.3	136.2	(137.7)	(136.5)	(137.4)	(139.4)	(137.8)
	135.3	136.2	(137.4)	(136.1)	(137.3)	(137.5)	(136.1)
C(2′)	135.3	136.2	(137.2)	(134.0)	(137.2)	(137.0)	(135.6)
C(2)	132.9	133.6	132.3	132.2	(136.5)	(136.5)	(134.5)
C=O	165.4	168.2	167.8	167.8	167.7	168.2	168.0
C(16)	95.1	95.9	105.7	104.7	96.2	102.3	101.1
C(17)	144.8	146.9	149.1	148.3	146.9	149.0	148.8

[a]) In ppm from internal TMS; similar values in parentheses may be interchanged.

Table 2. *^{13}C chemical shifts of model compounds* [a])

	6 [b]) $CDCl_3$	**7** [b]) $CDCl_3$	**8** [b]) $CDCl_3$	**9** [b]) [c]) DMSO	**10** [c]) $CDCl_3$	acetone	**11** [c]) acetone
Me(18)	14.5	18.0	18.2	22.3	22.9	21.1	(27.6)
Me(5′)							(27.2)
C(6)	21.3	16.8	21.3				
C(6′)				21.9	20.9	21.4	(22.2)
C(15)	30.1	30.8	24.8	18.3	19.4	20.7	(20.1)
C(14)	32.1	31.2	30.3				
C(20)	40.2	43.8	36.3	33.2	35.6	35.9	37.5
C(21)	56.2	46.8	55.2				
C(5′)				47.5	46.6	47.4	49.0
C(5)	52.7	50.9	52.8				
C(3)	59.8	53.8	55.2				
C(19)	73.3	75.3	74.7	53.5	54.6	55.0	56.9
C(7), (C(7′)) [d])	(106.1)	(107.4)	107.4	105.2	106.2	106.1	107.5
C(12), (C(12′))	110.6	111.1	110.5	110.9	111.0	111.5	111.8
C(9), (C(9′))	117.3	117.6	117.8	117.7	118.1	118.3	118.5
C(10), (C(10′))	118.4	119.1	118.7	118.4	119.2	119.2	119.4
C(11), (C(11′))	120.5	121.3	120.8	120.9	121.1	121.2	121.4
C(8), (C(8′))	126.6	127.3	126.6	126.1	127.7	128.3	128.2
C(13), (C(13′))	135.9	135.7	135.5	138.4	136.0	137.0	137.2
C(2), (C(2′))	134.0	132.4	134.0	135.9	139.7	141.1	140.2
C(16)	(106.5)	(107.7)	103.8	91.4	25.5	26.1	26.8
C(17)	154.5	155.9	154.8	145.4	48.3	48.9	41.1

a) In ppm from internal TMS; similar values in parentheses may be interchanged.
b) From reference [5].
c) For sake of clarity the carbon numbering system is that of rings E, A′, B′ and C′ of compounds **1**–**5**.
d) Numbering in parentheses refers to compounds **9**, **10** and **11**.

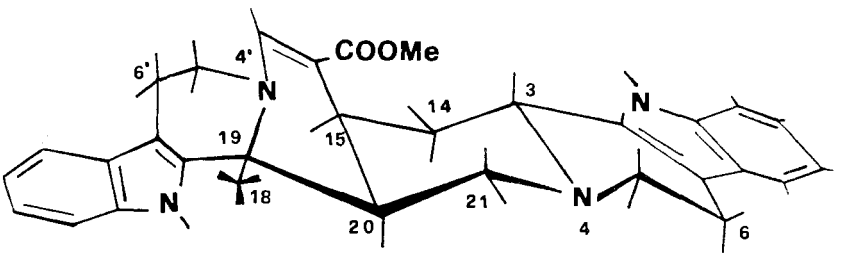
lack of the vicinal gauche interaction of C(21). Comparison of model **10** with **11**[5]) shows a trend for C(18) similar to that observed for roxburgine D and E.

Roxburghine C(**3**) has been identified as a *normal* ajmalicinoid system containing a C(19α)-methyl group [3] [4], a stereochemical pattern present in ajmalicine (**6**). The ^{13}C-NMR. spectra confirm this structure assignment. Expectedly, with the exception of C(15), the ring E, A′, B′ and C′ carbon atoms exhibit nearly the same shifts as like carbon atoms in roxburghine D(**1**). Finally, roxburghine C(**3**) reveals C(3) and C(6) shifts within the range of 60 ± 1 and 21.5 ± 0.5 ppm, respectively, characteristic of *normal* ajmalicinoid substances [5] as well as *ca.* 10 ppm deshielding of C(21) with respect to roxburghines D(**1**) and E(**2**).

5) The ^{13}C-shifts of **11** are in agreement with the expected ones and support the previous assignment [4] of a predominant *cis*-conformation with C(18) equatorial to ring E for this compound.

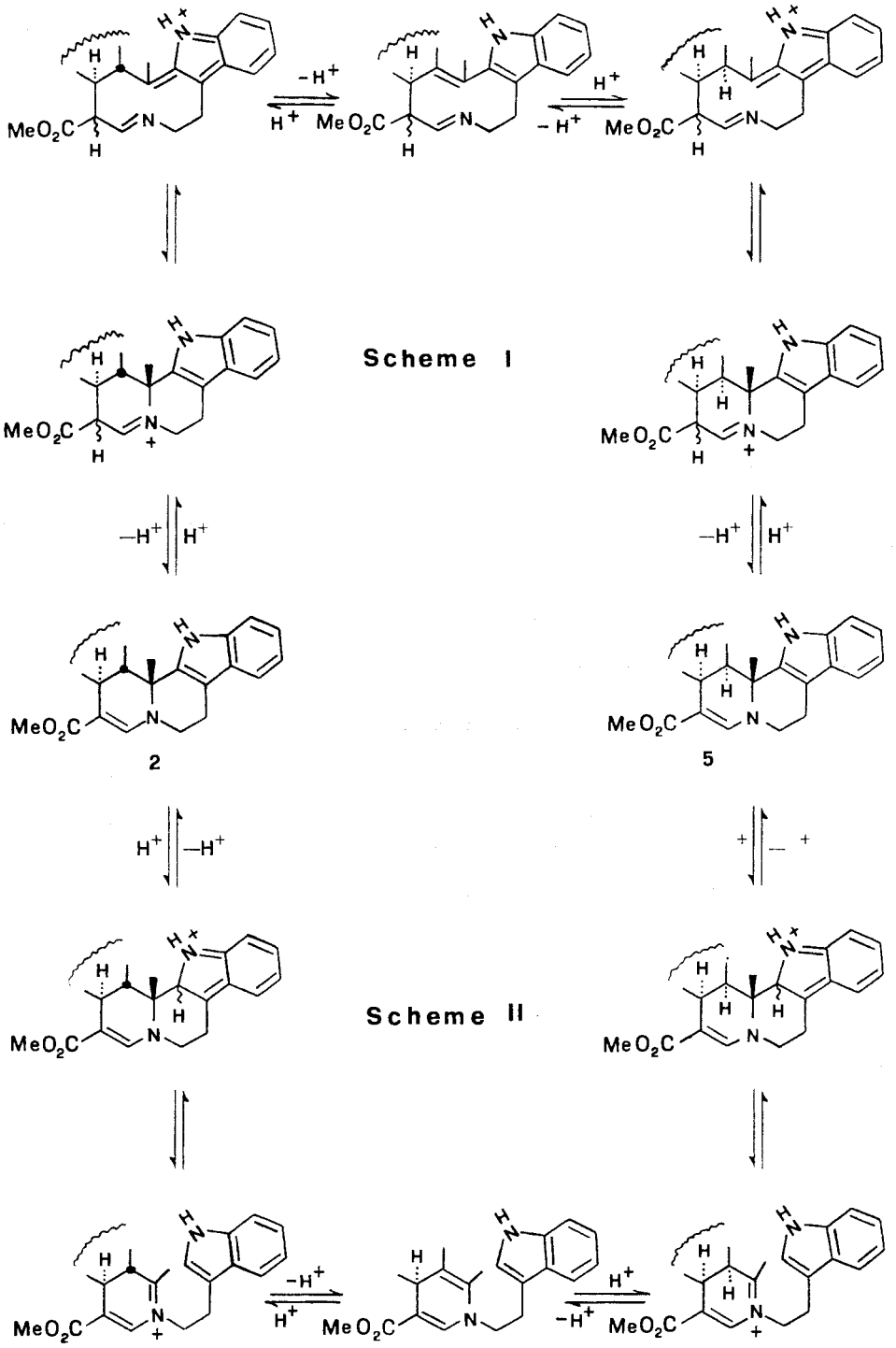
The unusual shielding of C(16) for roxburghines C(**3**) and D(**1**) and the compound **9** with respect to **6–8** is a result of the delocalization of the enamino nitrogen lone pair into the conjugated double bond >N–C(R)=C(R')–COOMe ↔ >N$^{\oplus}$–C(R)–C$^{\ominus}$(R')–COOMe. The low field shifts of C(16) and C(17) for roxburghine E(**2**) (and B) *vs.* roxburghine C(**3**) and D(**1**) can be interpreted with some steric inhibition to the conjugation. This is supported by the larger $\Delta\delta$ value observed for C(16), which is in position β to the enamino nitrogen atom. The different shieldings for each pair of isomers correspond to the change of configuration at C(19). As a matter of fact, examination of *Dreiding* models shows qualitatively that the increase of the planarity of N(4') involves an increase (resp. a decrease) of the non-bonded interactions for roxburghine E(**2**) and B (resp. D(**1**) and C(**3**)).

The ^{13}C-NMR, data of roxburghine B, especially the C(3) and C(6) shifts, mitigate against its suggested *normal* configuration [4]. In analogy with the δ values of C(3) and C(6) of the C/D *trans epi-allo* alkaloid akuammigine [**8**][6]) these shifts of roxburghine B fall within the range of 54.5 $\pm$ 0.5 and 21.5 $\pm$ 0.5 ppm, respectively, characteristic exclusively of *trans*-quinolizideine-containing *epi-allo* yohimboid and ajmalicinoid compounds [5]. The shifts of C(5) and C(14), carbon atoms unaffected by rings A', B' and C', are nearly identical with those of akuammigine (**8**). The methines of the D/E ring junction (C(15) and C(20)) of roxburghine B are shielded strongly with respect to the *normal* system, roxburghine C(**3**), in analogy with observations on *cis*– *vs. trans*-decalins [8] and the shift changes of C(15) and C(20) between ajmalicine (**6**) and akuammigine (**8**). Whereas $\Delta\delta_{15}$ is similar (5.7) to that between models **6** and **8** ($\Delta\delta_{15} = 5.3$), the $\Delta\delta_{20}$ value is larger (7.3 *vs.* 3.9) due to the added γ-effect of N(1'). (This effect is present in either C(19) configuration.) C(21) of roxburghine B is deshielded by *ca.* 5 ppm with respect to both roxburghine D(**1**) and E(**2**), whereas it is shielded by the same amount with respect to the *normal* roxburghine C(**3**). The similarity of the C(18) shift of roxburghine B and E suggests that the angular methyl group faces a similar environment in the two alkaloids. Being quasi-equatorial to ring E, the methyl group of **4** faces only one γ-effect from ring D and E carbons, *i.e.* C(21). The methyl group of roxburghine B experiences the same type of non-bonded



5a

6) Whereas akuammigine (**8**) at room temperature is a *ca.* 1:1 mixture of C/D *cis* and *trans epi-allo* conformers, the shifts in Table 2 and pertinent to the discussion are of the *trans*-quinolizidine form observed at low temperature [5].


Scheme I
Scheme II
2
5

interactions only on condition of being β-oriented. In this event it suffers a single γ-effect from a ring D or E site, *i.e.* C(21).

^{1}H-NMR. correlations on the conformation of the angular methyl group have been presented to show this function to be quasi-equatorial toward ring E in roxburghine B [4]. The combined NMR. data are in agreement with the unambiguous chemical correlation [3] with roxburghine D, that had established the C(18β) configuration for roxburghine B. Therefore this alkaloid must be represented by structure **5** and conformation **5a**. Independent ^{1}H-NMR. evidence for the same conclusions is reported in the foregoing paper [9].

Roxburghine E (**3**) has been converted to roxburghine B (**5**) on treatment with zinc in acetic acid [3]. This transformation has been interpreted to represent the isomerization of C(3) of **3** on the basis of the formulation **4** for roxburghine B. The new structure of the latter requires a mechanism of C(20) epimerization. *Schemes 1* and *2* constitute two possible alternatives for the reaction path.

Experimental Part. – The spectra have been recorded on a *Varian Associates* XL-100-15 spectrometer operating in the pulsed mode, using 8K data points in the time domain. The accuracy of the chemical shifts given in ppm relative to internal tetramethylsilane are accurate to 0.05 ppm. In order to enable comparison with literature data all experiments were carried out in deuteriochloroform (16 to 90 mg/0.3 ml depending on solubility and sample availability). Since Roxburghine C (**3**) and **11** are not stable in this solvent, measurements were also made in deuteriocetone allowing internal chemical shift comparison between the various isomers. The observed solvent shifts are negligible for aliphatic carbon atoms ($\Delta\delta_{max}$ 1.0–1.2). The slightly larger differences for the aromatic carbon atoms may be partly due to changes in concentration.

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