Tetrahedron Vol. 40, No. 24, pp. 5255 to 5261, 1984
Printed in the U.S.A

0040-4020/84 $3.00 + .00
Pergamon Press Ltd.

^{13}C NMR SPECTRA OF SOME AJMALANE ALKALOIDS[1]

B. DANIELI,* G. LESMA, G. PALMISANO and G. SEVERINI RICCA
Istituto di Chimica Organica della Facoltà di Scienze, Università
degli Studi di Milano, Centro di Studio per le Sostanze Organiche
Naturali del C.N.R., Via Venezian 21, 20133 Milano, Italy

(*Received in UK* 19 *January* 1984)

Abstract—An internally consistent set of carbon-13 assignments for ajmaline (**1**) and three diastereomers, isoajmaline (**2**), sandwicine (**3**) and isosandwicine (**4**), are presented.

Ajmalane alkaloids are a group of pentacyclic indoline compounds, structurally related to heteroyohimbines, which occur plentifully in many plants of *Aspidosperma, Rauwolfia* and *Tonduzia* genera. The most representative of these alkaloids is ajmaline (**1**) [(17*R*,21α)-ajmalane-17,21-diol] contained in large amount in the root bark of *Rauwolfia vomitoria* Afzel., whose intriguing structure has been the target of impressive chemical studies in the 1950s.[2]

Ajmaline (**1**) is therapeutically useful for the treatment of cardiac diseases. In particular, its 17-chloroacetyl derivative has been introduced in many European countries as antifibrillatory agent and *N*-(n-propyl)ajmalinium bitartrate is claimed to have considerable antiarrhythmic activity. Similar properties are exhibited by its stereoisomer isoajmaline (**2**) [(17*S*,20α,21β)-ajmalane-17,21-diol] whereas sandwicine (**3**) [(17*S*,21α)-ajmalane-17,21-diol] and isosandwicine (**4**) [(17*S*,20α,21β)-ajmalane-17,21-diol] seem devoid of therapeutical activity.

^{13}C NMR data of a few ajmalinoids have been reported for structural determination purposes. Chatterjee *et al.*[3] analysed the spectra of ajmalinoid alkaloids (e.g. rauflexine, vincamajorenine, majoridine and vincamajine) in comparison with that of ajmaline mainly in order to identify the location of the methoxy group on the aromatic ring in the former compound. Poisson *et al.*[4] examined the data of vomilenine and raucaffrinoline with respect to **1**, **2** and 17-acetyl-1-desmethyl-1,2-didehydroajmaline and concluded that raucaffrinoline has the same *trans*-arrangement of ring-D substituents at C-20/C-21 as in isoajmaline (**2**).

We report here the results of a detailed analysis of the ^{13}C spectra of the homogeneous series of geometrically defined diastereomers **1–4**. The data are of interest in view of the remarkable dependence of carbon shift on molecular geometry and substituent orientation within a system possessing a limited conformational flexibility, and permit the determination by rapid and direct analysis, of the relative stereochemistry at C-17, C-20 and C-21 of **1–4**, whose ^{1}H spectra are of little utility due to extensive overlap of signals.

Our results necessitate the revision of the C-20 shift for **1**, of the C-2, C-14, C-17 and C-21 shifts for **2** initially proposed by Chatterjee[3] and Poisson,[4] respectively, and allow the unambiguous assignment of C-3, C-5 and C-16 for **1** and **2**.

The study was limited to the differentiation of nonaromatic carbons. In fact, the shifts of all the *N*-methylindoline aromatic carbons duplicate those of the previously reported indoline bases and only slight differences among the isomers are observed.

Ajmaline (**1**)

Full assignment of ajmaline (**1**) (Table 1) based merely on known substituent effects on carbon shift is rather difficult due to the strong similarity of most carbons from each other as regards the field position and multiplicity. Thus, for unequivocal assignment, the functional and structural derivatives **1a–n** were examined. Acetates and their methiodides proved particularly useful to shift assignment in the parent compound and were extensively analysed with the aid of selective irradiation (Table 4) and by the observation of residual splittings and second-order effects.[5]

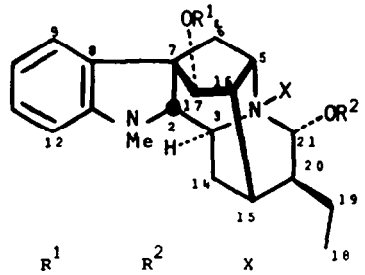
The nonaromatic carbons fall in three well-separated zones of the spectrum: in 77–88 ppm there are C-2, C-17 and C-21; in 43–56 ppm are present quaternary C-7 and C-3, C-5, C-16 and C-20 methines; below 35 ppm we found the remaining nonaromatic carbons.

Owing to the substitution by nitrogen and oxygen, C-21 appears the most deshielded methine, showing the expected shifts in methiodides[6] **1b** and **1d**, in *N*-oxides[7] **1f** and **1g**, but being surprisingly unaffected in the acetates **1c** and **1e**. The oxymethine C-17 lies furthest downfield compared with known similar oxygen-bearing carbons, whereas C-2 is expected to resonate in this region, as suggested by comparison with the same carbon in 1-methyl-deformyl-1,2-didehydroakuammiline.[8] A clear-cut distinction of the close C-2 and C-17 is based on the downfield shift of the latter on going from **1** to **1a**, **1c**, **1h**, **1j** and **1k**, in view of the well-known acetylation and etherification shift.[9] In **1c** and **1d**, the C-17 resonance is unequivocally determined by selective irradiation (Table 4). According to this assignment, the *N*-oxides **1f** and **1g** show an upfield shift of C-2 (in β-position

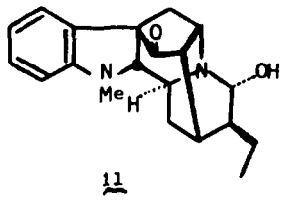
Table 1. ^{13}C Chemical shifts of ajmaline (1) and derivatives (1a–n) (25.2 MHz, $CDCl_3$)

Carbon	1	1a	1b	1c	1d	1e	1f [a]	1g	1h	1i	1j	1k	1l	1m	1n
2	79.3	79.3	77.3	79.3	77.0	79.3	77.4[c]	78.7	79.0	79.6	79.9	79.7	78.2	79.7	79.3
3	43.0	43.0	53.3	43.6	55.8	43.5	50.8	50.8	43.2	42.7	42.8	42.4	43.4[d]	47.8	49.3
5	52.8	52.9	62.2	53.5	64.8	53.6	64.5	66.8	53.1	53.0	53.3	53.1	50.3	55.1	56.1
6	34.8	35.5	32.0	36.1	32.0	35.2	31.6	32.1	35.5	35.5	36.3	36.1	34.9	35.2	36.1
7	56.1	54.7	53.3	54.4	55.2	55.9	53.8	53.5	55.2	56.1	55.5	55.5	59.1	53.4	53.8
8	133.3	132.0	129.1	132.1	128.9	133.4	132.4	129.3	132.4	133.8	133.9	133.7	129.0	131.2	132.1
9	122.8	122.3	122.9	122.3	122.9	122.8	123.2	122.7	123.1	122.8	123.4	123.3	122.3	122.4	122.4
10	119.0	119.0	120.8	119.2	120.8	119.2	118.2	119.3	119.0	119.2	119.2	119.1	120.0	119.2	119.2
11	127.1	127.5	128.6	127.6	128.7	127.2	126.8	128.2	127.1	127.1	127.0	127.0	128.0	127.7	127.5
12	109.5	109.6	110.4	109.6	110.6	109.5	108.1	109.7	109.3	109.5	109.3	109.2	109.9	109.5	109.6
13	153.6	153.6	152.2	153.8	152.4	153.8	153.2	153.2	153.5	153.9	153.9	153.9	153.6	153.3	153.9
14	31.4	31.3	30.2	31.8	30.5	31.8	29.4	30.7	28.8	32.1	32.1	32.0	32.9	31.6	29.2
15	28.3	27.9	26.6	27.3	25.8	27.4	27.6	26.0	28.1	28.4	29.0	29.1	29.3	26.8	28.0
16	45.2	43.0	44.9	43.0	45.4[b]	45.0	49.3	47.3	40.8	45.6	41.2	40.4	43.8[d]	44.5	50.3
17	77.3	80.2	78.3	80.0	78.1	77.3	77.2[c]	80.2	81.8	77.6	85.4	87.3	214.0	78.7	79.3
18	12.2	12.1	11.8	12.2	11.6	12.2	11.6	11.7	12.0	12.2	12.2	12.3	12.0	12.3	12.8
19	25.4	25.8	24.3	25.0	24.2	25.0	23.6	24.8	25.2	26.0	26.0	25.9	25.7	26.8	114.8
20	48.0	48.2	49.5	48.4	45.5[b]	48.0	52.4	50.8	47.5	48.3	48.5	48.5	47.1	38.5	139.3
21	88.1	88.5	95.2	88.7	92.1	88.8	[e]	102.4	88.1	94.6	94.7	96.3	88.7	51.8	55.3
N-Me	34.0	33.8	34.7	34.5	36.1	34.7	33.4	34.8	34.0	34.7	34.6	34.6	34.0	33.9	34.4
N^+Me			45.5		48.3										
OCOMe		21.3	21.2	21.1 21.2	21.1 21.5	21.1		21.2							21.3
OCOMe		170.2	170.1	168.8 170.2	168.1 170.2	169.1		170.3							170.3
OMe												56.3 56.7			
OEt										64.2 15.7	64.0 64.3 15.5 15.4				

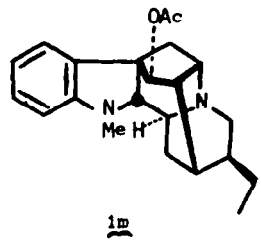
[a] DMSO-d_6 ; [b,c,d] Signals may be reversed ; [e] Signal not detected



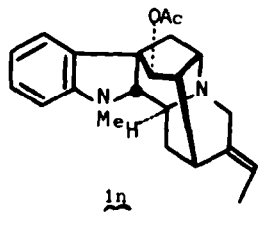
	R^1	R^2	X	
1	H	H	-	
1a	Ac	H	-	
1b	Ac	H	Me	I^-
1c	Ac	Ac	-	
1d	Ac	Ac	Me	I^-
1e	H	Ac	-	
1f	H	H	O	
1g	Ac	H	O	
1h	CH_2SMe	H	-	
1i	H	Et	-	
1j	Et	Et	-	
1k	Me	Me	-	



1l

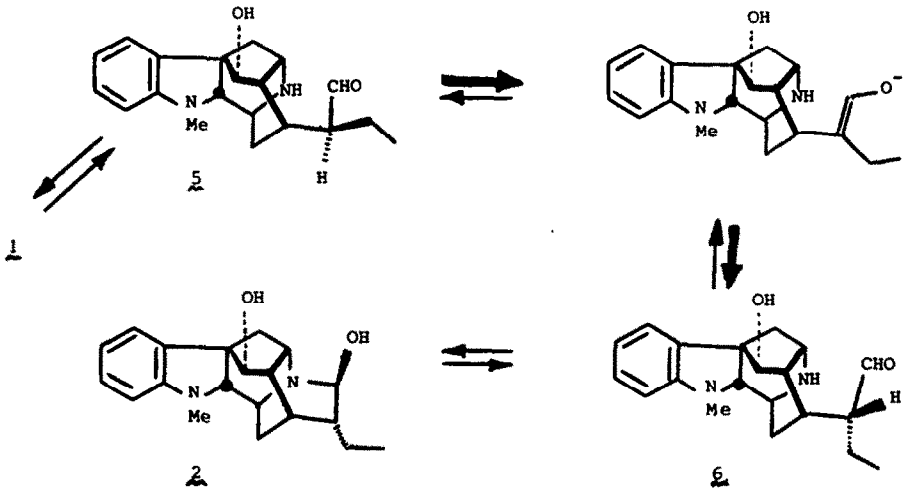


1m



1n

to nitrogen) whilst C-17 is invariant. Conversely, both C-2 and C-17 are shifted upfield in the methiodides **1b** and **1d**, indicating the strong dependence of carbon shifts on subtle conformational changes throughout the rigid carbon skeleton. In all compounds, C-15 is unquestionably the highest field methine, almost unaffected by any substitution and structural modification. It is noteworthy to point out that the unsubstituted methines C-16 and C-20 lie in the same zone as the aminomethines C-3 and C-5, in spite of their β-position to heteroatoms. The C-5 signal is easily recognisable near 53 ppm by application of selective irradiation on acetates **1a–d**, suffering a large shift on N_b-oxidation and N_b-quaternization. The signal near 48 ppm exhibits a broad doublet in off-resonance spectra by virtue of long-range C–H interactions and second-order effects. By this criterion, this signal is attributed at C-20 in the parent ajmaline and its derivatives and it exhibits the expected upfield shift on quaternization and *N*-oxide formation. In 21-deoxyajmaline derivative **1m**, C-20 appears upfield in the zone of methylene carbons due to the lack of C(21)–OH. The assignment of the close signals at 43.0 and 45.2 ppm to C-3 and C-16, respectively, in ajmaline (**1**) deserves some comment. The former is not substantially affected in the acetates and ethers, whereas the latter suffers an upfield shift upon acetylation and etherification at C(17)–OH. The two resonances are clearly distinguishable in methiodides and *N*-oxides, although C-16 shows a small but unexpected downfield shift. In addition, the absence of the α-oriented OH at C-21 in **1m** causes the elimination of a 1,3 γ-interaction with C-3 which, in turn, suffers a downfield shift. Moreover, the oxidation of C(17)–OH in **1** to ajmalidine **11** leaves C-3 unaffected and C-16 surprisingly shielded in sharp contrast



Scheme 1.

with the known perturbation accompanying the oxidation of alcohol to carbonyl compound. Further support to this assignment comes from the spectrum of 2 which will be discussed below.

In the zone below 35 ppm a distinction is required only for C-6, C-14 and C-19 methylenes. The more upfield methylene at 25.4 ppm belongs to C-19 as suggested by the appearance of a broad triplet in the off-resonance spectrum due to long-range C–H couplings and second-order effects, by the disappearance in the spectrum of 17-acetyltetraphyllicine **1a** and by analogy with the same signal in similar compounds such as dregaminol and tabernaemontanol.[10] C-6 and C-14 are both β to nitrogen and experience the same shift on quaternization and *N*-oxidation, whilst the assignment of 34.8 and 31.4 ppm signals, respectively, is possible only by inspection of the spectrum of **2**.

Isoajmaline (2)

Base-catalysed treatment of ajmaline (**1**) induces inversion at C-20 through the intermediacy of the open-chain aldehyde **5**. Ring closure of the isomeric aldehyde **6** furnishes the natural isoajmaline (**2**), in which the β-orientation at C-21 is dictated by relief of 1,2-steric compression between the OH and the ethyl chain (Scheme 1). The new chirality at C-20/

Table 2. ^{13}C Chemical shifts of isoajmaline (2) and derivatives (**2a–d**)[a]

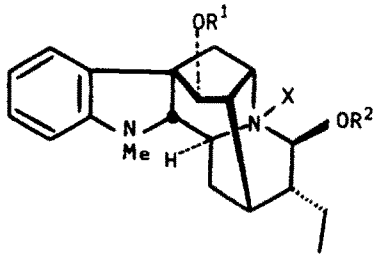
Carbon	2	2a	2b	2c	2d
2	78.7	79.0	77.3	78.7	77.1
3	47.5	47.8	56.4	48.1	58.8
5	48.0	48.2	58.4	49.8	61.0
6	34.1	35.2	31.6	35.7	32.2
7	55.6	54.7	53.3	54.3	52.9
8	133.7	131.9	129.0	132.0	129.0
9	123.1	122.3	122.8	122.4	122.8
10	118.5	119.1	120.6	119.2	120.7
11	126.5	127.4	128.6	127.6	128.7
12	108.6	109.6	110.4	109.6	110.6
13	153.4	153.6	152.3	153.8	152.2
14	22.3	22.6	21.9	22.0	21.5
15	29.1	29.0	27.6	29.7	27.3
16	53.0	51.1	51.3	51.0	51.5
17	75.9	79.6	77.6	79.4	77.7
18	12.3	12.3	11.7	12.0	11.3
19	25.6	25.6	25.1	25.6	25.4
20	45.2	45.1	43.6	43.3	44.4
21	87.4	88.2	95.7	87.6	90.2
N-Me	34.0	34.1	34.7	34.5	35.3
N^+-Me			45.4		46.6
OCOMe		21.3	21.2	21.2 21.4	21.2 21.5
OCOMe		170.4	170.1	169.8 170.2	168.2 170.1

[a] At 25.2 MHz in $CDCl_3$

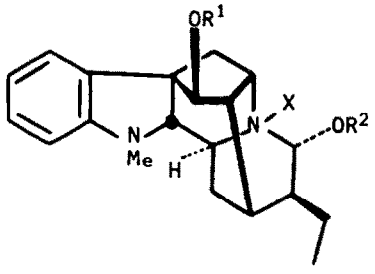
C-21 strongly modifies steric interactions in the molecular framework with remarkable effects on shifts of some carbons. In comparison with **1**, C-14 is expected upfield due to 1,3 γ-interaction with C-19, whereas C-16 should suffer a downfield shift. The above effect induced by the ethyl orientation resembles that on the same carbons on going from the related tabernaemontanine to dregamine.[10] Analogously, C-5 is expected upfield by γ-interaction with C(21)–OH and C-3 should move downfield. Full assignment of the spectrum of **2** (Table 2) has been possible by analysis of a few derivatives (e.g. acetates **2a**, **2c** and the corresponding methiodides **2b**, **2d**) taking advantage of the same criteria developed for **1**. In the 88–77 ppm region, the signals at 78.7 and 75.9 ppm are attributed to C-2 and C-17, respectively, on the basis of the same argument as for **1**. In the 55–45 ppm zone, the more upfield signal at 45.2 ppm is C-20 and the lower field methine at 53.0 ppm is C-16. The remaining signals at 48.0 and 47.5 ppm are due to both C-3 and C-5 and their close proximity agrees with the above expectations (downfield and upfield, respectively, in comparison with ajmaline). The assignment reported in Table 2 parallels that on the acetates where it is substantiated by selective irradiation (Table 4). Below 35 ppm, C-19 is easily recognized, invariant with respect to **1** as a consequence of the replacement of the γ effect exerted by C-16 by one of comparable magnitude by C-14. The last mentioned carbon is the most upfield methylene at 22.3 ppm suffering a nearly identical shift as C-16, but in opposite direction. C-6 is invariant with respect to the configurational changes and both C-6 and C-14 have the same quaternization shift as in ajmaline (**1**).

Sandwicine (**3**) *and Isosandwicine* (**4**)

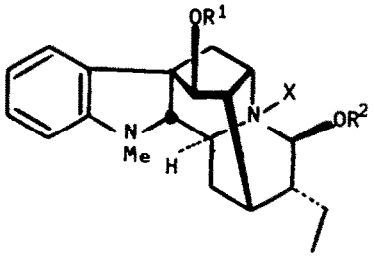
These compounds differ from ajmaline (**1**) and isoajmaline (**2**) in the absolute configuration at C-17, which is (*S*) instead of (*R*). As a consequence, the



	R^1	R^2	X	
2	H	H	-	
2a	Ac	H	-	
2b	Ac	H	Me	I^-
2c	Ac	Ac	-	
2d	Ac	Ac	Me	I^-



	R^1	R^2	X	
3	H	H	-	
3a	Ac	H	-	
3b	Ac	H	Me	I^-
3c	Ac	Ac	-	



	R^1	R^2	X	
4	H	H	-	
4a	Ac	H	-	
4b	Ac	H	Me	I^-
4c	Ac	Ac	-	
4d	Ac	Ac	Me	I^-

Table 3. ^{13}C Chemical shifts of sandwicine (3), isosandwicine (4) and their derivatives[a]

Carbon	3	3a	3b	4	4a	4b	4c	4d
2	75.7	77.1	75.4	76.3	76.1	75.3	76.3	76.3
3	44.8	43.7	54.6	48.1	48.1	58.3	48.7	60.8
5	53.0	52.4	62.0	48.6	48.4	57.9	49.5	60.0
6	34.9	35.3	31.3	35.1	33.7	31.4	35.5	31.5
7	54.0	53.3	52.7	54.5	53.3	53.1	53.0	52.3
8	131.8	130.9	128.3	131.8	129.9	129.0	131.0	128.7
9	120.3	120.7	121.2	119.6	120.4	120.6	120.2	121.2
10	118.7	118.9	120.8	118.8	119.4	119.9	119.5	120.7
11	127.1	127.4	128.8	127.3	127.9	128.1	127.5	128.0
12	109.7	109.2	110.6	109.5	109.6	109.9	109.5	110.5
13	153.3	153.3	152.4	153.9	152.9	152.5	153.5	152.3
14	31.0	32.1	31.4	22.3	22.1	22.0	21.9	21.6
15	27.2	27.4	26.2	28.2	28.8	27.5	29.5	27.0
16	34.4	33.7	36.1	43.4	41.6	42.4	42.1	42.3
17	70.8	73.6	71.5	72.3	72.9	71.5	73.6	71.3
18	12.1	12.1	12.0	12.4	12.1	11.8	12.1	11.4
19	25.0	25.7	24.4	25.8	25.9	26.2	25.2	26.2
20	48.7	48.8	49.1	45.6	44.8	43.7	43.7	44.4
21	88.1	88.5	95.6	88.1	88.0	96.2	87.6	90.6
N-Me	34.4	34.3	35.3	34.5	34.1	35.3	34.9	35.7
N^+Me			44.7			44.9		45.3
OCOMe		21.0	21.0		20.9	21.0	(21.4/21.0)	(21.5/20.9)
OCOMe		170.3	170.0			170.1	169.8 170.1	169.7 168.4

[a] At 25.2 MHz in $CDCl_3$

Table 4. ^1H Chemical shifts at 100 MHz($CDCl_3$) of selected derivatives

Compound	H-2[a]	H-3[b]	H-5[c]	H-17	H-21
1a	2.74	3.62	3.01	5.28[d]	4.23[f]
1b	2.80	3.96	4.28	5.18[d]	5.15[f]
1c	2.68	3.60	3.02	5.22[d]	5.25[f]
1d	2.91	4.46	4.84	5.20[d]	5.92[f]
2a	2.60	3.30	3.56	5.17[d]	3.96[g]
2b	2.82	4.52	4.08	5.14[d]	5.28[g]
2c	2.70	3.57	3.46	5.25[d]	5.26[g]
2d	2.88	5.33	4.58	5.16[d]	6.25[g]
3a	3.09	3.78	2.90	5.68[e]	4.20[f]
3b	3.16	4.09	4.15	5.75[e]	5.18[f]
4a	3.10	3.60	3.65	5.70[e]	4.10[g]
4b	3.17	4.83	4.07	5.77[e]	5.31[g]
4c	3.03	3.68	3.39	5.66[e]	5.26[g]
4d	3.28	5.34	4.60	5.84[e]	6.22[g]

[a]broad singlet; [b]broad doublet (J = 9 Hz); [c]multiplet (underlined values are doublet of doublets with J = 6.5 Hz); [d]broad singlet ($W_{1/2}$ = 2.5 Hz); [e]doublet (J = 9 Hz); [f]broad singlet ($W_{1/2}$ = 5 Hz); [g]broad doublet (J = 7 Hz).

orientation of C(17)–OH is expected to influence the shifts of the carbons in the pentatomic system together with C-2, C-3 and C-14. The data reported in Table 3 were obtained with the help of acetates **3a**, **4a**, **4c** and methiodides **3b**, **4b** and **4d**.†

Both C-2 and C-17 in **3** and **4** are shifted upfield by comparison with **1** and **2**, the latter signal exhibiting the usual shift on acetylation. In the 55–45 ppm zone of **3**, only three methine signals are present, C-5 (53.0 ppm), C-20 (48.7 ppm) and C-3 (44.8 ppm), and are easily recognized by inspection of **3a** and **3b** spectra, nearly unaffected with respect to **1**. The missing C-16 methine resonates at 34.9 ppm, very close to C-6 methylene and this assignment is unequivocally confirmed by the upfield shift of this signal in **3a** and by a downfield shift in **3b**. The origin of the dramatic shielding of C-16 on changing the orientation of an OH group on neighbouring carbon could be rationalized in terms of steric interaction between eclipsed C(17)–OH and C(16)–H bonds.

In isosandwicine (**4**), C-16 falls into the middle part of the spectrum (55–43 ppm) suffering the expected downfield shift on inversion of ethyl chain orientation at C-20. A choice between C-3 and C-5 in **4** can be made by the observation of the invariance of these signals when compared with 17-acetyl derivative (**4a**). Furthermore, the downfield shift of both these carbons in 17,21-diacetylisosandwicine (**4c**) parallels that of isoajmaline serie.

Finally, the shift assignment of the remaining carbons in **3** and **4** follows the same arguments as for ajmaline (**1**) and isoajmaline (**2**).

† Unfortunately, it was not possible to utilize the spectrum of 17,21-diacetylsandwicine (**3c**). The sample furnished us by the authors of Ref. 11 showed a single spot in TLC under various conditions, however its ^{1}H and ^{13}C spectra were due to a mixture of two main products. We have no plausible and convincing explanation for this spectroscopic behaviour, in spite of the fact that **3c** was obtained by acetylation of pure **3a** (checked by ^{13}C spectrum) by usual protocol.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at 25° C on a Varian XL-100 spectrometer at 100 MHz (CW mode) and 25.2 MHz (FT mode), respectively. All samples were run in 0.05–0.5 M deuteriochloroform unless stated otherwise. For ^{13}C spectra the data acquisition conditions for the free induction decay were: pulse width 10 μs, acquisition time 0.8 s (with a spectral width of 5000 Hz), pulse delay 0.5 s. The shifts are in ppm downfield from Me_4Si.

Acknowledgement—The authors are deeply indebted to Inverni della Beffa, Milan, for sample of all the cited compounds.

REFERENCES

[1]Preliminary communication: B. Danieli, G. Palmisano and G. Severini Ricca, *Tetrahedron Letters* 4007 (1981).
[2]For a recent review on ajmaline alkaloids, see: A. Koskinen and M. Lounasmaa, In *Progress in the Chemistry of Organic Natural Products* (Edited by W. Herz, H. Grisebach and G. W. Kirby), Vol. 43, p. 267. Springer-Verlag, Wien (1983).
[3]A. Chatterjee, M. Chakrabarty, A. K. Ghosh, E. W. Hagaman and E. Wenkert, *Tetrahedron Letters* 3879 (1978).
[4]F. Libot, N. Kunesch and J. Poisson, *Phytochemistry* **19**, 989 (1980).
[5]E. W. Hagaman, *Org. Magn. Reson.* **8**, 389 (1976).
[6]W. O. Crain Jr., W. C. Wildman and J. D. Roberts, *J. Am. Chem. Soc.* **93**, 990 (1971).
[7]E. Wenkert, H. T. A. Cheung, H. E. Gottlieb, M. C. Koch, A. Rabaron and M. M. Plat, *J. Org. Chem.* **43**, 1099 (1978).
[8]B. C. Das, J.-P. Cosson and G. Lukacs, *J. Org. Chem.* **42**, 2785 (1977).
[9]F. W. Wehrli and T. Wirthlin, *Interpretation of Carbon-13 NMR Spectra*, p. 37. Heyden, New York (1976).
[10]E. Bombardelli, A. Bonati, B. Gabetta, E. M. Martinelli, G. Mustich and B. Danieli, *J. Chem. Soc. Perkin Trans. I* 1434 (1976).
[11]F. Ronchetti, G. Russo, E. Bombardelli and F. Bonati, *Phytochemistry* **10**, 1385 (1971).