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^{13}C NMR SPECTROSCOPY OF PYRROLIZIDINE ALKALOIDS

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Key Word Index—^{13}C NMR; pyrrolizidine alkaloids; retronecine; pyrrolizidine *N*-oxides.

Abstract—The ^{13}C NMR spectra of nine pyrrolizidine alkaloids of the macrocyclic diester type, seven of the corresponding *N*-oxides and of the parent base retronecine have been recorded and the signals assigned. The ^{13}C NMR signals were found to be sensitive to structural variation in both the diester moiety and the heterocyclic ring system, providing useful information for structural elucidation, particularly when the ^{1}H NMR spectra may be difficult to interpret.

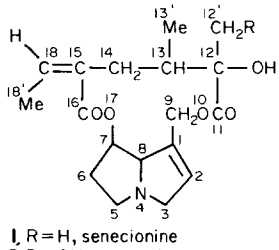
INTRODUCTION

Pyrrolizidine alkaloids, particularly those of the macrocyclic diester type, which occur in the genus *Senecio*, and to a lesser extent in a number of other genera, present a hepatoxicity hazard to range animals and potentially to humans [1]. A continuing survey being conducted by this laboratory of a large number of *Senecio* species growing in the western United States, both uninvestigated and previously investigated, has yielded known alkaloids together with generally small amounts of unknown alkaloids of apparently similar structural type. Since ^{1}H NMR spectra of the latter provided only limited information in regard to slight structural variation in the necic acid portion of the molecule, due to overlapping or obscured signals, it became essential to obtain ^{13}C NMR spectral data for known alkaloids in order to provide additional information for structural elucidation.

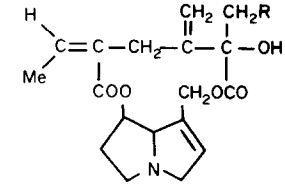
Most of the ^{13}C NMR spectra previously reported have been limited to individual compounds, lacking rigorous derivation of assignments [2–5], or to partial assignments of only the carbonyl and α,β-unsaturated carboxyl groups [6–8]. More recent publications on the ^{13}C NMR of four macrocyclic pyrrolizidine alkaloids by Drewes *et al.* [9] and of several macrocyclic and non-macrocyclic pyrrolizidine alkaloids by Mody *et al.* [10] report assignments which differ in significant respects from our results. Moreover, certain obviously incorrect assignments for retrorsine [11] have been perpetuated by citation in a reference volume of ^{13}C NMR shift assignments of alkaloids [12]. We now report the ^{13}C NMR spectra and systematic derivation of signal assignments for a number of pyrrolizidine alkaloids of closely related structural types, together with certain of their *N*-oxides, in order to provide the correlations necessary for interpretation of the spectra of novel alkaloids.

RESULTS AND DISCUSSION

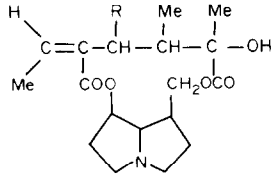
The ^{13}C NMR spectral data are reported in Table 1 for senecionine (**1**), retrorsine (**2**), seneciphylline (**3**) and riddelliine (**4**), the most typical and frequently encountered pyrrolizidine alkaloids of *Senecio* species, together with retronecine (**10**), the necine base common to the above and many other alkaloids of this type. In addition, assignments are listed for the dihydropyrrolizidines platphylline (**5**) and hygrophylline (**6**) as well as the *seco*-type, senkirkine (**7**). These 12-membered macrocyclic ring alkaloids have been numbered in accordance with the system proposed by Culvenor *et al.* [13], extended by the addition of appropriate numbering for carbon atoms substituent



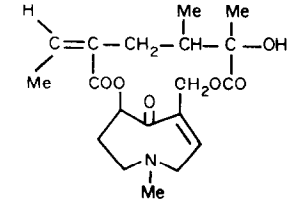
1 R = H, senecionine
2 R = OH, retrorsine



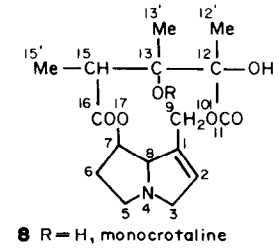
3 R = H, seneciphylline
4 R = OH, riddelliine



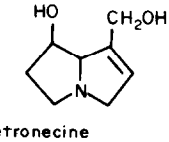
5 R = H, platyphylline
6 R = OH, hygrophylline



7 senkirkine



8 R = H, monocrotaline
9 R = COMe, spectabiline



10 retronecine

Table 1. ^{13}C NMR data for pyrrolizidine alkaloids

Carbon	1	2	2*	3	3*	4	4*	5	6	7†	8‡	9§	10	10*
1	133.1	132.5	132.9	131.5‖	132.2	131.2‖	132.1	39.7	40.8	134.3	132.8	132.9	137.8	140.1
2	136.6	136.7	134.7	136.5	134.9	136.6	135.2	31.5	29.3	137.4	134.3	134.3	127.2	123.4
3	62.9	62.8	62.3	62.8	62.3	62.7	62.4	53.7	54.7	64.4	61.3	61.1	61.9	62.1
5	53.1	53.0	52.6	53.2	52.6	53.2	52.7	51.9	52.4	53.1	53.6	53.7	54.2	53.5
6	34.8	34.7	34.2	34.8	34.2	34.7	34.3	35.7	35.2	37.7	33.6	32.6	35.3	36.0
7	75.0	75.0	74.5	74.8	74.3	75.0	74.6	74.2	75.5	78.1	75.1	73.2	71.0	70.0
8	77.6	77.5	76.9	77.6	76.8	77.4	76.9	69.3	69.8	192.4	76.9	78.0	79.4	77.9
9	60.6	61.1	58.9	60.9	58.9	61.6	59.5	66.4	64.6	58.5	60.5	59.5	58.6	58.3
11	178.1	175.6	174.2	176.7	174.7	174.2	172.8	178.6	178.0	178.0	174.0	174.2	—	—
12	76.7	81.4	81.0	76.2	75.8	79.2	79.3	75.9	78.2	76.6	76.8	76.7	—	—
13	38.4	35.7	35.3	146.3	147.9	143.3	144.9	37.3	41.7	38.6	78.8	85.6	—	—
14	38.3	37.9	37.2	37.4	36.9	37.6	37.3	39.2	73.3	36.4	44.3	43.5	—	—
15	131.5	131.3	131.9	131.4‖	131.5	131.1‖	131.4	131.8	133.4	131.9	—	—	—	—
16	167.5	167.3	166.8	166.9	166.3	166.9	166.4	167.6	166.9	166.4	173.5	168.8	—	—
18	134.0	134.6	132.9	135.9	134.9	135.9	134.9	135.9	134.8	137.0	—	—	—	—
12′	25.0	66.9	66.6	24.8	24.4	66.2	65.8	26.2	25.6	24.6	22.0	21.3	—	—
13′	11.1	11.7	11.1	114.1	111.4	114.5	112.2	13.4	5.7	10.9	17.7	16.9	—	—
18′	15.0	15.0	14.7	15.1	14.7	15.2	14.8	15.5	15.0	15.3	—	—	—	—

The spectra were obtained at *ca* 30° in $CDCl_3$ solutions unless otherwise noted. The δ values are in ppm downfield from TMS.

*Spectra obtained in DMSO-d_6 solutions.

†δ(N–Me) = 40.4 ppm.

‡δ(C-15′) = 13.7 ppm.

§δ(C-15′) = 14.1 ppm. δ(COMe) = 169.4 and 16.9 ppm respectively.

‖Signals may be interchanged.

to the macrocyclic ring, as shown for senecionine (**1**). The 11-membered macrocyclic ring alkaloids monocrotaline (**8**) and spectabiline (**9**), which occur in *Crotalaria* species, have been numbered in a similar manner but with a disjunction at C-14 in order to facilitate comparison of chemical shifts with those of the 12-membered macrocyclic group. Data are also reported in Table 2 for the *N*-oxides of retronecine (**10**) and the six pyrrolizidine alkaloids (**1–4**, **8** and **9**).

Assignments of the ^{13}C NMR signals were achieved by a combination of techniques, involving examination of proton noise-decoupled and proton-coupled spectra, comparison of spectra of alkaloids having closely related structures, application of standard chemical shift theory and shift reagents, [14, 15]. The spectra of several alkaloids were obtained in both $CDCl_3$ and d_6-DMSO in order to provide information regarding possible changes in chemical shift with solvent, in the event that alkaloids of unknown structure might be insufficiently soluble in $CDCl_3$ and the spectra of the *N*-oxides were obtained in D_2O.

Retronecine (**10**)

This alkaloid is the most frequently occurring necine base comprising the fundamental heterocyclic ring system of the pyrrolizidine alkaloids. It is common to all of the compounds under consideration with the exception of platyphylline and hygrophylline, which are closely related dihydroretronecine derivatives, and senkirkine, a *seco*-derivative. Since consideration of the arguments advanced for assignment of signals in previously published data [9, 10] for retrorsine indicated that certain of these were incorrect, its spectrum was analysed in detail.

The lowfield resonances at 137.8 and 127.2 ppm are readily assigned to the unsaturated C-1 and C-2 atoms respectively and distinguished by the singlet for the former and doublet for the latter in the proton-coupled spectrum. The two methine carbon resonances may be assigned by consideration of the deshielding effect of the allylic double bond on C-8 which therefore gives rise to the lower-field resonance at 79.4 ppm, whereas the secondary alcoholic C-7 is responsible for the signal at 71.0 ppm.

Of the four triplets due to methylene resonances in the proton-coupled spectrum the two higher-field signals at 35.3 and 54.2 ppm must be due to C-6 and C-5 respectively, from standard chemical shift considerations. The remaining resonances at 58.6 and 61.9 ppm have been assigned to C-3 and C-9 respectively [9, 10] but these assignments are neither in accord with ^{13}C NMR data for other types of alkaloids containing saturated and unsaturated five-membered ring systems [14] nor with the data presented by Mody *et al.* [10] in a comparison of retronecine with its diacetate.

On the basis of these results, acetylation produces an upfield shift of 4.1 ppm for C-1 and a downfield shift of 2.5 ppm for C-3, which is remote from the position of acetylation at C-9, resulting in an unexpectedly small shift of +1.0 ppm for the latter in comparison to the C-7 alcoholic group which shows a shift of +2.9 ppm. Reversal of the original assignments would result in much more consistent shift values of −0.7 for C-3 and +4.2 ppm for C-9.

In order to confirm that the published assignments for these two positions were incorrect, the ^{13}C NMR spectrum of retrorsine was determined with sequential additions of *tris*(6,6,7,7,8,8,8-heptafluoro-2,2-

Table 2. ^{13}C NMR data for pyrrolizidine alkaloid *N*-oxides

Carbon	*N*-oxides						
	1	**2**	**3**	**4**	**8***	**9†**	**10**
1	133.8	133.4	132.2	131.9	132.0	131.5	138.7
2	140.6	141.1	142.4	142.4	134.3	135.0	122.5
3	80.5	80.2	80.3	80.3	79.4	79.5	80.7
5	71.0	70.9	71.0	71.0	69.4	68.9	71.0
6	35.3	35.3	35.2	35.2	34.0	33.3	36.6
7	76.7	76.7	76.3	76.6	75.0	73.9	72.2
8	98.2	98.0	98.1	98.0	96.8	97.0	97.8
9	62.2	62.5	62.6	63.2	62.1	62.4	60.8
11	180.3	178.0	178.5	176.4	178.6	178.4	—
12	80.4	84.8	79.5	82.5	79.0	79.2	—
13	41.2	38.5	149.0	145.9	82.0	88.5	—
14	40.4	40.1	39.4	39.8	45.1	45.0	—
15	131.3	131.2	131.2	131.2	—	—	—
16	171.5	171.1	170.7	171.1	177.4	173.3	—
18	134.2	134.5	134.1	134.4	—	—	—
12′	26.7	69.1	26.6	68.3	23.9	23.3	—
13′	13.1	13.6	116.9	117.7	19.8	19.2	—
18′	17.5	17.5	17.6	17.6	—	—	—

The spectra were obtained at *ca* 30° in D_2O solutions.
*δ(C-15′) = 15.8 ppm.
†δ(C-15) = 16.3 ppm. δ(COMe) = 175.7 and 18.8 ppm respectively.

dimethyl-3,5-octanedionato)ytterbium, [Yb(fod)$_3$]. Three resonances showed much larger shifts at all concentrations of shift reagent, with correspondingly greater broadening of the signals, indicating that the reagent was interacting with the nitrogen atom. These resonances therefore correspond to the C-3, C-5 and C-8 atoms, exhibiting shifts of + 184, + 187 and + 192 ppm respectively, whereas the other signals show shifts of only 102–128 ppm, at a Yb(fod)$_3$/retronecine molar ratio of 0.144.

The resonance for C-3 is therefore easily distinguished from that of C-9, and the correct assignments are 61.6 and 58.3 ppm as shown in Table 1. The assignment of all ^{13}C NMR resonances for retronecine thus provides a foundation for the analysis and interpretation of the corresponding spectra of the much more complex pyrrolizidine alkaloids.

Senecionine (**1**), *retrorsine* (**2**), *seneciphylline* (**3**) *and riddelliine* (**4**)

These four compounds are probably the most cosmopolitan of the pyrrolizidine alkaloids, one or more occurring in a large number of species of *Senecio* [1]. They form a coherent group varying only in the substitution at C-12′ and in the degree of unsaturation of the C-13–C-13′ bond and for this reason present an ideal group whereby ^{13}C NMR assignments may be made by comparison of compounds having closely related structures.

As might be expected, the resonances attributable to C-3, C-5, C-6 and C-8 in all four alkaloids have quite similar values to those of the parent base retronecine (**10**), differing by not more than 2.0 ppm, since these atoms are well removed from the esterifying diacid moiety. The C-7 and C-9 atoms show shifts to lower field of 3.8–4.0 and 2.0–3.0 ppm, respectively, induced by esterification of the alcohol functions. The major significant variations between retronecine and the alkaloids occur for the resonances of C-1 and C-2 which exhibit large shifts of 4.7–6.6 ppm upfield and 9.3–9.5 ppm downfield, respectively. Examination of molecular models of these 12-membered macrocyclic ring alkaloids in the generally accepted conformation [1, 16] reveals coplanarity of the carbonyl group and the double bond, with resultant close proximity of the C-11 carbonyl group to C-1 and especially C-2. Such stereochemical interactions could account for the above shifts.

Assignment of the resonances for the ester carbonyl groups can be made with ease since in all four alkaloids the α,β-unsaturated C-16 resonance occurs at 166.9–167.5 ppm, whereas the unconjugated C-11 carbonyl resonance occurs at lower field, namely 174.2–178.1 ppm [15]. The greater range in values for the latter is probably a reflection of the different substituents at C-12′ which are in close enough proximity to affect the environment of the ester function.

The assignment of resonances to most of the carbon atoms in the necic acid moieties can be made by comparison of the spectra of these four alkaloids. However, the olefinic carbons at C-15 and C-18 present a particular problem since the resonances are close to those of C-1 and C-2, and show corresponding multiplicities in the proton-coupled spectra. The resonance of C-2 was assigned for senecionine by using the difference selective population inversion pulse sequence technique to give pseudo-INDOR spectra [17]. Excitation of the low-field H-2–^{13}C satellite showed coupling to the ^{13}C signal at 136.6 ppm and the resonance at 134.0 ppm can therefore be assigned to C-18. Assignments for C-1 and C-15 cannot be readily made but comparison with the ^{13}C

NMR spectra of monocrotaline (**8**) and spectabiline (**9**), which lack the C15–C-18 double bond, indicate that the C-1 resonance should fall at *ca* 133 ppm. The C-1 resonance in senecionine is therefore assigned to the signal at 133.1 ppm and that of C-15 to the signal at 131.5 ppm. Correspondingly consistent assignments for C-1, C-2, C-15 and C-18 can be made for retrorsine (**2**). In the case of the latter alkaloid, the only member of this group for which data have been previously reported, the results presented in Table 1 differ from those derived by Casal *et al.* for nine positions and by Mody *et al.*[10] for eight positions. However, they are in agreement with the assignments of Drewes *et al.* [9], with the exception of the interchange of the values for C-3 and C-9, corresponding to the correction of these assignments for retronecine, as previously discussed.

The ^{13}C NMR spectra of retrorsine, seneciphylline and riddelliine were also measured in DMSO-d_6, in order to obtain data which would be applicable to pyrrolizidine alkaloids too insoluble for their spectra to be obtained in $CDCl_3$. The majority of the resonances were found to be quite similar for all 3 alkaloids in both solvents except those for C-2, C-9, and C-11, and in seneciphylline and riddelliine, C-13 and C-13′, which show appreciable shifts, ranging from 1.4 to 2.7 ppm. This effect may well be a result of disruption by the DMSO of intramolecular hydrogen-bonding with the C-11 carbonyl group, resulting in a somewhat different conformation of the macrocyclic ring and consequently different environments for the adjacent carbon atoms which exhibit shifts.

Platyphylline (**5**) *and hygrophylline* (**6**)

The assignment of the ^{13}C NMR resonances for the previous four alkaloids simplifies the assignment for these two representatives of the dihydropyrrolizidine group. Comparison of the spectra of senecionine (**1**) and platyphylline (**5**), which differ only in the C-1–C-2 bond, shows differences of generally less than 1 ppm for all carbon atoms not α- to either C-1 or C-2, with the exception of C-13′. Surprisingly, this methyl group shows a downfield shift of 2.3 ppm in platyphylline and examination of molecular models provides no obvious explanation for this shift.

It remains to assign resonances only for those carbon atoms affected by saturation of the 1,2-double bond in senecionine, namely C-1, C-2, C-3, C-8 and C-9. Of the two methine carbon atoms, C-1 and C-8, the latter, being adjacent to the nitrogen atom, must correspond to the lower field signal at 69.3 ppm and C-1 therefore is assigned to the resonance at 39.7 ppm. The C-3 methylene gives rise to a signal at 53.7 ppm, close to that of C-5, since both atoms lie in a similar environment. The position of C-9, adjacent to the ester oxygen atom results in its signal occurring at the lowfield position of 66.4 ppm and the remaining resonance at 31.5 ppm is consequently assignable to C-2.

The spectrum of platyphylline (**5**) provides additional confirmation for the assignments of the C-1, C-2, C-15 and C-18 olefinic carbon atoms in senecionine (**1**) and the other 1,2-unsaturated alkaloids. Thus, the signals for C-15 and C-18 show close correspondence in both compounds since these atoms are well removed from the positions of structural variations in the heterocyclic ring and assignments for the olefinic C-1 and C-2 atoms can be made by a process of elimination.

The spectrum of hygrophylline (**6**) shows little variation from that of platyphylline (**5**), apart from the signals attributable to those carbon atoms adjacent to the site of hydroxyl substitution at C-14, the signal for the latter exhibiting the expected large downfield shift to 73.2 ppm when compared with platyphylline. The assignments for C-7, C-8 and C-14 reported by Drewes *et al.* [9] do not correspond well with those derived for platyphylline and the pyrrolizidine alkaloids (**1–4**), the values shown in Table 1 being much more consistent.

Senkirkine (**7**)

This compound presents an interesting variation on the structure of normal pyrrolizidine alkaloids, being a *seco*-derivative in which the C-8–N-4 bond of the heterocyclic ring is cleaved to give a C-8 carbonyl group and an N-4 methyl group. In other respects the molecule is identical to senecionine (**1**).

Despite this rather radical structural alteration, the resonances for the macrocyclic diester moiety show little variation from those of senecionine, the most significant being a rather unexpected 3.0 ppm downfield shift for C-18, and a 1.9 ppm upfield shift for C-14. However, X-ray crystallographic data [18] indicates that although the heterocyclic ring portion has a quite similar folded conformation in both molecules, intramolecular hydrogen-bonding of the C-12 hydroxyl group to the C-8 carbonyl in senkirkine produces an entirely different relationship of C-14 and C-18 to the ester carbonyl C-16 as compared to senecionine, which may account for the observed shifts.

Even those carbon atoms adjacent to the point of cleavage do not exhibit particularly radical changes, C-6 and C-7 showing downfield shifts of 2.9 and 3.1 ppm, respectively, and C-9 being shifted upfield by 2.1 ppm. In comparison with senecionine a new signal is present at 40.4 ppm corresponding to the N–Me group, while the signal due to C-8 is absent, being replaced by a carbonyl resonance at 192.4 ppm. The position of the latter signal is particularly significant since it occurs at the normal position for an α,β-unsaturated carbonyl group and thus provides additional evidence that, although the transannular N–C distance is only 2.297 Å, the corresponding partial bond is not particularly significant. In fact, the bond number has been calculated to be 0.05 [18]. Two other *seco*-pyrrolizidine alkaloids for which partial ^{13}C NMR data has been reported, namely ligularidine [7] and syneilesine [6], have α,β-unsaturated carbonyl resonances at 193.7 and 189.4 ppm respectively, the shift of the latter to somewhat higher field possibly indicating greater transannular interaction with the nitrogen atom. Additional ^{13}C NMR data from other alkaloids exhibiting transannular N–C=O interaction, particularly clivorine which has an N–C distance of 1.993 Å and a calculated bond number of 0.15 [18, 19], may provide further information as to the range of such interactions and their role in physiological activity.

Monocrotaline (**8**) *and spectabiline* (**9**)

These compounds differ from those previously discussed in possessing an 11-membered rather than a 12-membered macrocyclic ring. Nevertheless, the resonances for the carbon atoms in the retronecine moiety show very little variation from those observed previously, the most significant being that due to C-2 which exhibits an upfield shift of 2.3 ppm relative to the signal for the same atom in senecionine (**1**).

The ester carbonyl groups at C-11 and C-16, however, show significant shifts of 4.1 ppm upfield and 6.0 ppm downfield, respectively, for monocrotaline as compared to senecionine, probably as a result of the more limited conformational possibilities imposed on the smaller macrocyclic ring. Acetylation of the C-13 hydroxyl group to give spectabiline (**9**) produces little effect on the C-11 resonance but shifts that of the C-16 upfield by 4.7 ppm, possibly due to removal of hydrogen-bonding between the –OH and –C=O groups. The assignments for all other carbon atoms in these two alkaloids can be made quite unequivocally, including those of the acetate group in spectabiline (Table 1).

Pyrrolizidine alkaloid N-*oxides*

Despite the fact that macrocyclic diester pyrrolizidine alkaloid *N*-oxides frequently comprise the major portion of these alkaloids in nature [20], their ^{13}C NMR spectra have not been recorded, with the exception of those of retronecine and monocrotaline *N*-oxides recently reported by Barreiro *et al.* [21].

Table 2 records the ^{13}C NMR data for the *N*-oxides of senecionine (**1**), retrorsine (**2**), seneciplylline (**3**), riddelline (**4**), monocrotaline (**8**), spectabiline (**9**) and retronecine (**10**), measured in D_2O. These results accord with those reported [21] for retronecine *N*-oxide but comparison of the spectra for spectabiline and monocrotaline *N*-oxides indicates that the assignments for C-12 and C-13 in the latter should be interchanged.

As expected C-3, C-5, and C-8 show large deshielding effects in the spectra of the *N*-oxides, compared to the tertiary bases, whereas the other carbon atoms show relatively minor shifts. In the macrocyclic diester *N*-oxides, C-8 exhibits the largest downfield shift, ranging from 19.0 to 20.6 ppm. For retronecine *N*-oxide, the smaller shift of 18.4 ppm emphasizes the effect of esterification upon this position. The C-3 position shows little variation in shift, ranging from 17.4 to 18.4 ppm but the shift of C-5 produced on *N*-oxidation is significantly different for the 11-membered macrocyclic alkaloids monocrotaline and spectabiline (15.2–15.8 ppm) relative to the 12-membered macrocyclic alkaloids (17.4–17.9 ppm). This effect is undoubtedly due to the different conformations imposed upon the C-11 and C-12 necic acid moieties by diesterification with the necine base. Other smaller shifts produced on *N*-oxidation are most significant for the C-11 and C-16 ester carbonyl groups and for those atoms of the ester portion of the molecule which extend over the necine moiety.

The assignments presented for the *N*-oxides in Table 2, in addition to confirming those derived for the free bases, provides correlations whereby the tertiary bases and their *N*-oxides can be readily distinguished by the use of ^{13}C NMR spectroscopy.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded at 25.03 MHz. 16000 data points were used to cover a spectral width of 6250 Hz. Samples were pulsed every 2 sec with a flip angle of 45°.

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