CARBON-13 NUCLEAR MAGNECTIC RESONANCE SPECTROSCOPY OF QUINOLIZIDINE DERIVATIVES[1]

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I. INTRODUCTION

The quinolizidine nucleus (1) is contained in many compounds of biological and medicinal interest, and presents an interesting conformational problem due to the presence of the mobile nitrogen atom (fig 1).

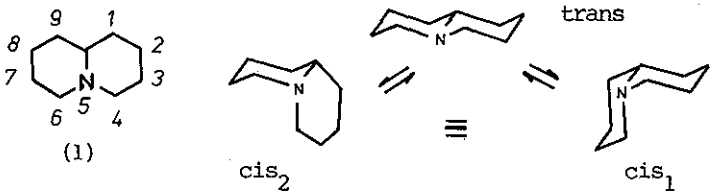


Fig 1 : Conformational equilibrium in quinolizidine (1).

The determination of the configuration and the conformation of substituted quinolizidines by infrared and proton magnetic resonance spectroscopy has been reviewed by Crabb[2,3]. The influence of the nitrogen lone pair on these spectra is mainly confined to the adjacent protons.

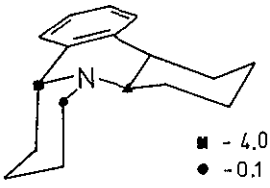
The ^{13}C NMR spectrum allows the observation of the whole molecular skeleton, while its sensitivity to stereochemistry has been amply demonstrated[4,5]. A large amount of ^{13}C data has now been accumulated on quinolizidine derivatives, part of which is contained in reviews on naturally occurring substances[6,7,8]. We will mainly discuss the influence of the cis or trans nature of the ringfusion, and the influence of the lone pair orientation on the ^{13}C spectra.

II 1. EFFECTS ASSOCIATED WITH THE NITROGEN AND ITS LONE PAIR

A number of specific effects associated with the nitrogen and its lone pair have been observed, mainly in saturated nitrogen heterocycles.
These effects are also found in quinolizidines.

a. α-Carbons

Apart from a sizeable downfield effect, due to the inductive effect of the nitrogen[9], the suggestion was made[10] that in trans-fused quinolizidines the α-carbons are deshielded by the overlap between the nitrogen lone pair and the antibonding orbital of the adjacent axial C-H bond. Since no such evidence is found on changing the quinolizidine ring fusion in other compounds, such as (2) and (3), the observation is probably due to an incorrect assignment[7] (see 55). An interchange of the aminomethylene chemical shifts, gives the shifts of the α-carbons on changing a trans- to a cis-quinolizidine shown in (4). These are comparable to the ones found between trans- and cis-decalin(5).



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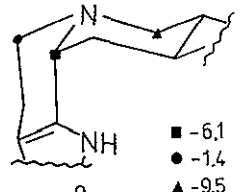

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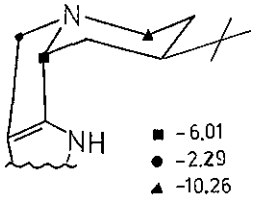

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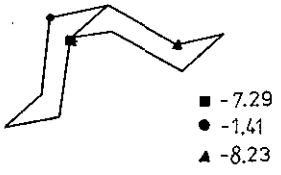


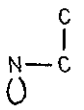
(5)[12]

Fig 2 : Δδ(trans-cis) of α-carbons

b. β-Carbons

The β-carbons are slightly shielded, compared to their position in the carbocyclic analogs, which is explained by the alternations of charge polarisation due to the nitrogen atom[9]. Several authors have reported sizeable upfield shifts of β-carbons which are antiperiplanar to the lone pair (6)[13-17].

The exact mechanism of this shielding effect is not clear however[18], since it



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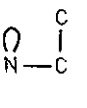


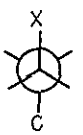
(7)

is absent in NH compounds.

The eclipsing of C_β by the lone pair (7) has no large shielding effect[19].

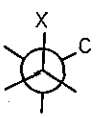
c. γ-Effects

γ-Carbon atoms located anti to a nitrogen atom (8a) are shielded with respect to the analogous carbons anti to a methyl or a methylene group (8b)[20]. A γ-gauche nitrogen (9a) also has a shielding effect which is greater than the upfield shift caused by a methyl or a methylene group (9b). The incremental upfield shift on the gauche carbon is generally less than the corresponding upfield shift on the anti carbon. This has been explained by a hyperconjugative transfer of charge from the free-electron pair to the trans γ-atom[20], although a back-lobe overlap mechanism should also be considered[21].



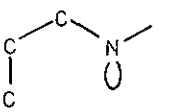
(8a) X=N

(8b) X=CH_2 or CH_3



(9a) X=N

(9b) X=CH_2 or CH_3



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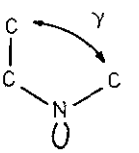


(11)

The effect is at least partly transmitted through the bonds[13], which results in an increased shielding of C-2 in quinolizidine ($\Delta\delta$=-2.41 ppm with respect to trans-decalin[12]), since it is doubly γ to N.

The γ-effect of the lone pair (10) is of the same order as that of a C-H bond[7,16], no deshielding influence by the lone pair[22] is observed.

One might expect that the γ-effect between C_β and C_α, as in (11) would be large due to the short C-N bond length. Evidence for this is found in (12), compared to (13), and on comparing the C-21 chemical shifts of yohimbine and pseudo-yohimbine (3)[6,7].

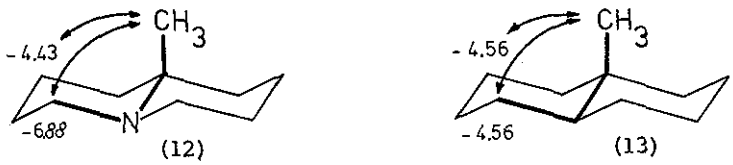
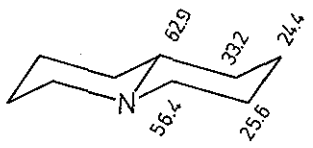


Fig 3 : Methylsubstituent effect on γ-carbons

II 2. ALKYLQUINOLIZIDINES

The ^{13}C spectrum of quinolizidine has been investigated by several authors[6,15,23-25] and assigned by comparison with piperidine derivatives and with the 3,3-dideuterio derivative[6]. Eight monomethylquinolizidines were studied by LaLonde[25], and their chemical shifts were compared with those of the trans-decalins. The decalin and quinolizidine chemical shifts are nearly



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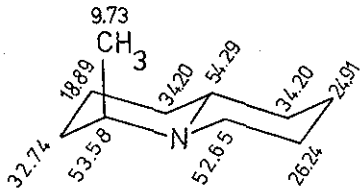


(14)

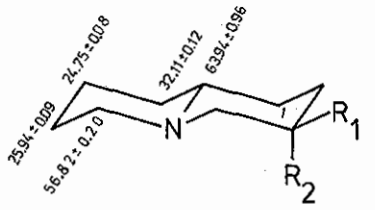
interchangeable for all ring carbons, when an adjustment is made for the chemical shift differences due to CH by N replacement. The quinolizidine chemical shifts can be calculated from the corresponding decalin shifts using equation 1.

$$\delta_{quin.} = A\delta_{decal.} + B \quad (eq\ 1)^{25}$$

carbon position	Values for constants A	B
α	1.013	21.16
α_B	1.034	17.51
β	0.975	-0.41
γ	0.977	-1.64

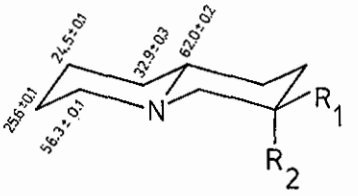
The A and B constants were determined for the α, β and γ-carbons. The use of these parameters for larger ring systems was illustrated by the determina-

§ The reported chemical shifts[6,15,23-25] differ slightly from each other, mainly due to the different recording conditions.



(15)[27]

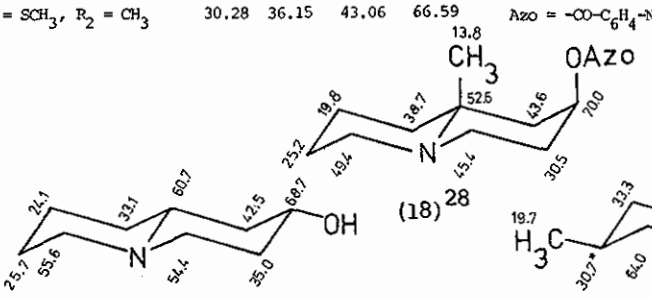
	δC_1	C_2	C_3	C_4
$R_1 = CH_3$, $R_2 = CH_2SCH_3$	29.82	35.71*	35.20*	66.71
$R_1 = CH_2SCH_3$, $R_2 = CH_3$	29.84	35.70	35.70	66.69
$R_1 = SCH_3$, $R_2 = CH_3$	30.28	36.15	43.06	66.59



(16)[28]

	δC_1	C_2	C_3	C_4
R_1 = OAzo, R_2 = H	31.3	30.4	70.8	59.9
R_1 = H, R_2 = OAzo	28.6*	28.4*	67.7	58.8

Azo = -CO-C_6H_4-N=N-C_6H_5 (p)



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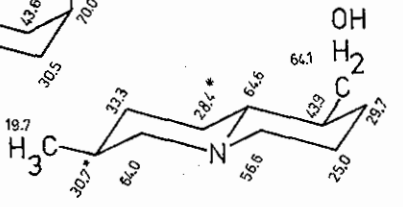

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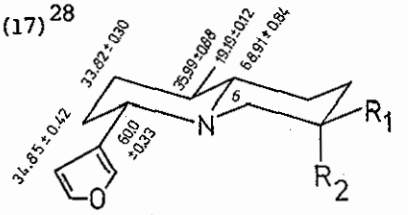

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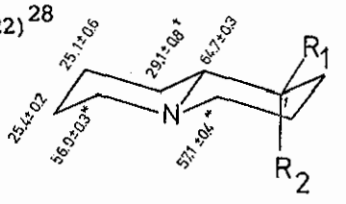
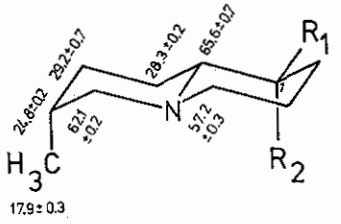


(19)[27]

	δC_6	C_7	C_8	C_9	CH_3
$R_1 = H$, $R_2 = CH_3$	58.19	28.66	30.56	25.74	17.57
$R_1 = CH_3$, $R_2 = H$	61.47	31.19	33.71	30.34	20.13
$R_1 = OH$, $R_2 = CH_3$	63.45	69.48	30.55	28.21	25.48
$R_1 = CH_3$, $R_2 = OH$	63.57	67.11	36.94	26.87	26.26

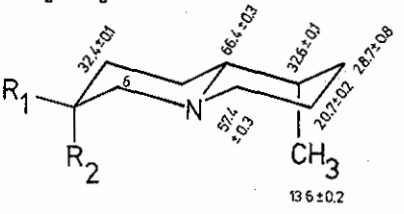
(20)[24]

	δC_1	C_2†	C_3	CH_2
$R_1 = CH_2OH$, $R_2 = H$	43.8	29.5	24.9	64.1
$R_1 = CH_2OBz$, $R_2 = H$	41.0	29.6	24.2	66.5
$R_1 = H$, $R_2 = CH_2OH$	38.8	30.8	22.6	64.7
$R_1 = H$, $R_2 = CH_2OBz$	38.4	27.5	24.5	64.5



(21)[28]

	δC_1	C_2	C_3	CH_2
$R_1 = CH_2OH$, $R_2 = H$	42.9	30.0	24.6	64.5
$R_1 = H$, $R_2 = CH_2OH$	38.5	31.7	22.9	65.8



(23)[28]

	δC_6	C_7	C_9	CH_2
$R_1 = CH_2OH$, $R_2 = H$	60.7	39.0	28.1	65.8
$R_1 = H$, $R_2 = CH_2OH$	59.4	34.8	26.6	65.7

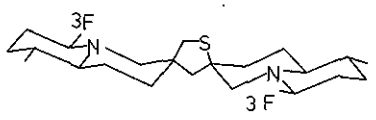
*,† Throughout this paper, chemical shifts marked with these signs may have reverse assignments.

tion of the conformational equilibrium in tripiperideine[26].

The spectrum of the ninth t-4-methyl isomer (14)[15] confirms the trans-conformation, which has been a matter of discussion for long. The very high field position of the methyl in (14) is ascribed to the β-antiperiplanar lone pair effect. The difference in chemical shift between axial and equatorial methyls which is different for each position on the ring, is however not well understood[27].

Several other trans-fused quinolizidines with varying substituents (15-23) have been studied. In general the substituent effects on the quinolizidine ring carbons parallel those in the carbocyclic series, although the magnitude is different for each substituent position.

Model compounds (15) and (19) were used to interpret the spectra of the C_{30} Nuphar alkaloids (24-26)[27,29] and of their sulfoxides[30], all with trans-fused quinolizidines.



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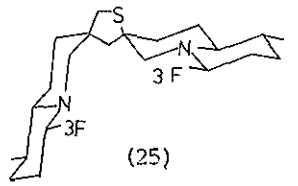

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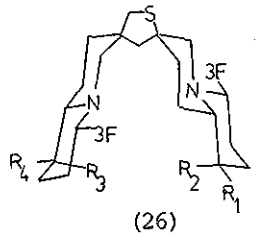


(26)

a $R_1=R_4=CH_3$, $R_2=R_3=H$

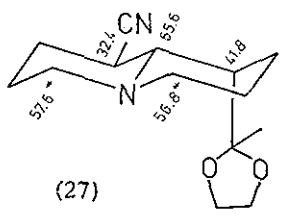
b $R_1=R_4=H$, $R_2=R_3=CH_3$

c $R_1=R_3=H$, $R_2=R_4=CH_3$

d $R_1=R_3=CH_3$, $R_2=R_4=H$

3F =

Wenkert[24] detected the cis-quinolizidine-conformation on comparison of even a partial assigment of the signals in the isomeric compounds (27-28).



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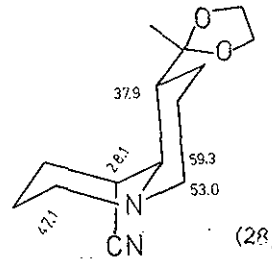

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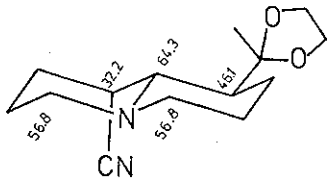

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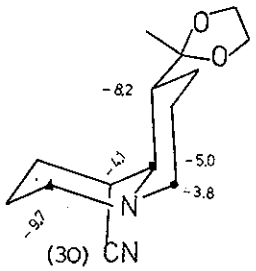
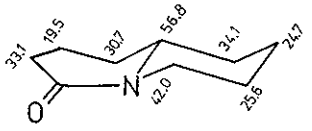


(30) : $\Delta\delta$ (29-28)

In the cis-conformation, the angular carbon and the γ-interacting carbons are shifted upfield (see (30)), in agreement with the observations in decalin (5)[12].

Some 4-oxoquinolizidine derivatives (31-33) were studied as models for lupin alkaloids[28].



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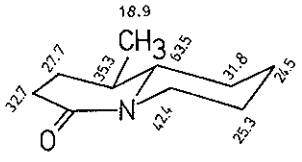

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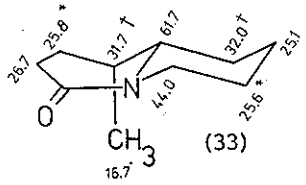
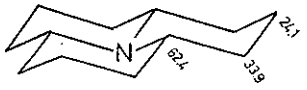


(33)

The spectra of the perhydropyrido[2,1,6-de]quinolizine isomers (34) and (35) were reported[31]. The assignments can be made by comparison with quinolizidine (1) and by considering the influence of changing the ringfusion (6).



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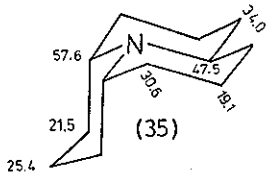
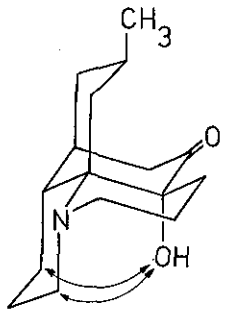


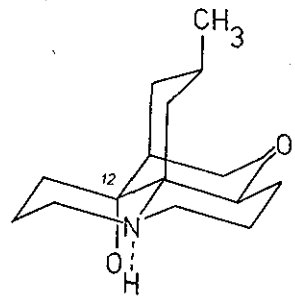
(35)

II 3. LYCOPODIUM AND LUPIN ALKALOIDS

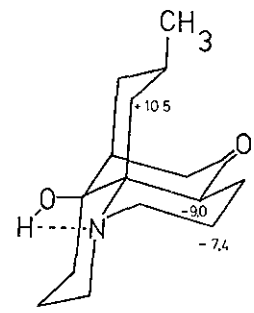
The lycopodium alkaloids lycopodine, dihydrolycopodine, epidihydrolycopodine, flabelliformine (36), clavolonine, α-lofoline, alkaloid L-23 (37) and lycodoline (38) were studied by ^{13}C NMR[32]. Most of them contain a cis-quinolizidine nucleus. The inversion of configuration at C-12 between (37) and (38) results in change from a trans- to a cis-quinolizidine ring fusion, with the accompanying characteristic shifts indicated on (38). In flabelliformine



δ (36)



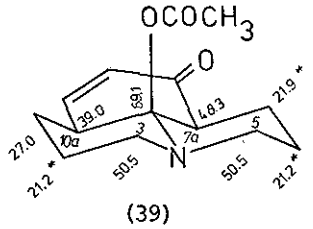
(37)



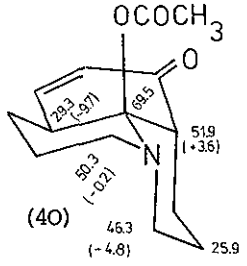
(38)

(36), the syn-axial hydroxyl group with respect to C-9 and C-11 results in the now well documented[33] deshielding δ-interaction. The chemical shift assignments in these compounds were corroborated by titration experiments with CD_3COOD (vide infra).

The power of ^{13}C NMR spectroscopy for monitoring the stereochemistry of intermediates in the synthesis of lycopodium bases was illustrated for a number of tricyclic compounds (39-40)[24]. By considering only the methine and the aminomethylene chemical shifts, a distinction between the trans,trans (39) and the trans,cis (40) hydrojulolidine configurations can be made. The upfield shift of C-10a establishes the configuration (40) and combined with the absence of such a shift on C-7a, excludes (41)[34].



(39)



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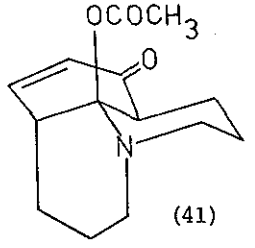
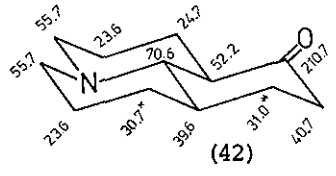
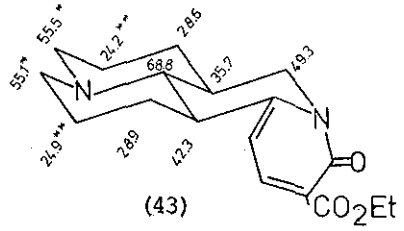


(41)

A number of trans,trans-fused hydrojulolidones (e.g. (42)) served as model compounds for the interpretation of the spectra of the carbomethoxy compounds (39,40), and allowed the determination of the stereochemistry of the isophoramine derivative (43).

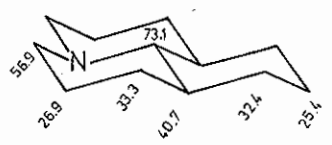


(42)

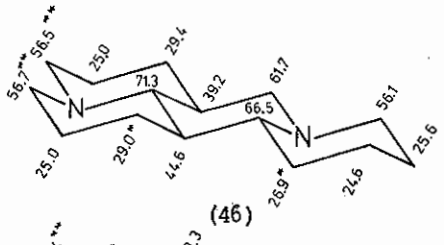


(43)

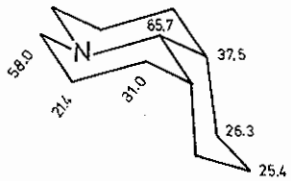
The two isomeric hexahydrojulolidines (44,45) served as models for the study of matrin-derivatives (46,47)[28], and their 15-keto compounds. The steric in-



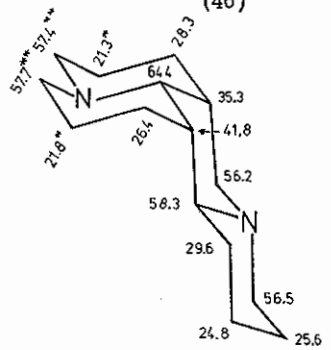
(44)



(46)

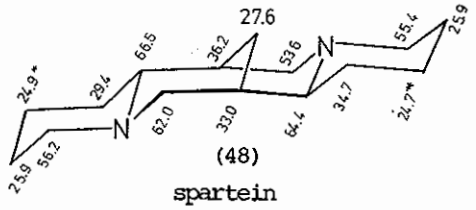


(45)

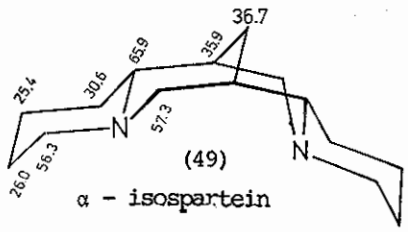


(47)

fluence of the lone pair is visible in these isomers. It is also evident in spartein (48), where its bowsprit-flagpole interaction shifts C-8 strongly upfield from its value in α-isospartein (49).



(48)
spartein



(49)
α - isospartein

The substituent effects of a hydroxyl or a keto group in these compounds are consistent with those found in other alicyclic systems.

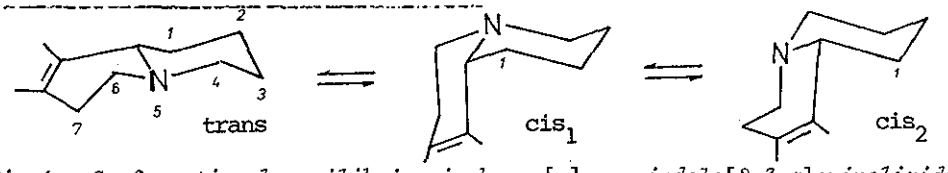
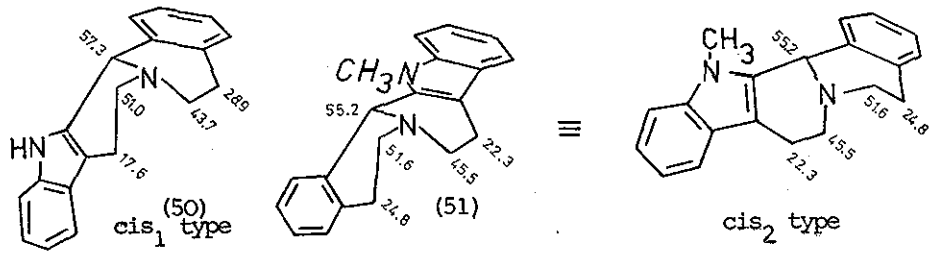
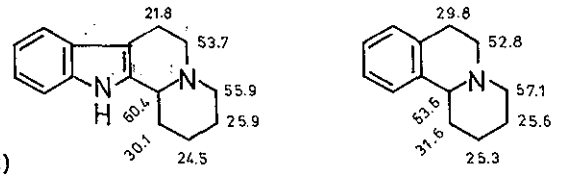


Fig 4 : Conformational equilibrium in benzo[a]- or indolo[2,3-a]quinolizidine

The trans and the cis_1 quinolizideine[35] conformations can be distinguished by the characteristic chemical shift of C7 : 21-22 ppm in the trans-versus 16-18 ppm in the cis_1 indolo [2,3-a] compounds[7], and 29-30 ppm vs 24-25 ppm in the cis benzo [a] compounds. The high field position of C7 in the indolo-compounds has been ascribed to the high electrondensity at the indole carbons[10]. At the same time, the angular quinolizideine carbon is shifted upfield by ca 6 ppm in the cis conformations (cf 3,4). In the cis_2 conformation, the aminomethylene C6 is shifted upfield, while C7 has the same chemical shift as in the trans-conformation. The difference between the two types of cis-conformations, as well as between a benzo- and an indolo-substitution can be seen in (50) and (51)[36].

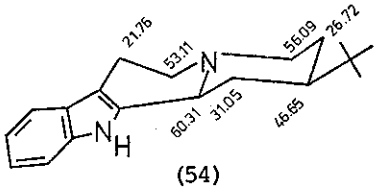


The parent compounds indolo [2,3-a]- and benzo [a]-quinolizidine (53) have a trans-conformation, which is clearly shown by their chemical shift values.

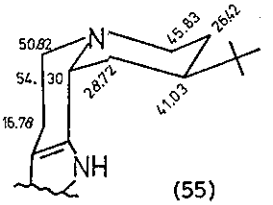


The assignment of the resonances in (52) was confirmed[37] by the study of six of its deuterated derivatives[10]. The two 2-t-butyl epimers have a trans-(54) (⩾95%) and a cis-(55) (⩾99.9%) conformation. The t-butyl holding group allows the study of the effect of the quinolizideine ring fusion on the ^{13}C chemical

shifts[10]. For reasons mentioned in II 1a, the assignment of the aminomethylenes in (55) was reversed.

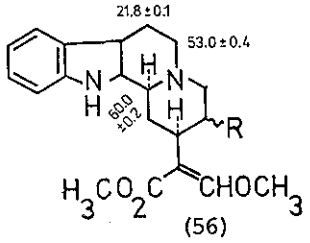


(54)



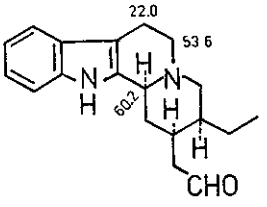
(55)

Several other ring D-substituted derivatives of the corynantheioid type (56-57)[6] and the ochrolifuanines (58)[38] were studied. All these have trans-conformations.

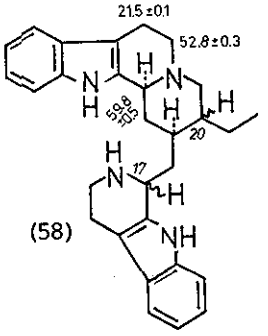


(56)

R = α-CH=CH$_2$ corynantheine
R = α-CH$_2$CH$_3$ dihydrocorynantheine
R = β-CH$_2$CH$_3$ corynantheidine



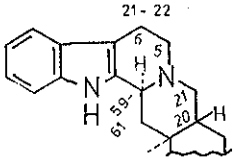
(57)



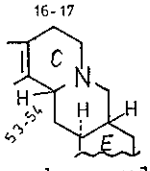
(58)

a 17βH, 20βH
b 17αH, 20βH
c 17βH, 20αH
d 17αH, 20αH

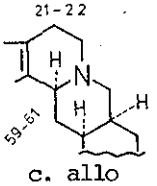
From an extensive study of stereoisomers of yohimboid and ajmalicinoid alkaloids (59), Wenkert[7] was able to show that the chemical shifts of C-3 and C-6 can be used for configurational and conformational assignments[39]. These characteristic values are shown on (59a-c). In the epiallo compounds



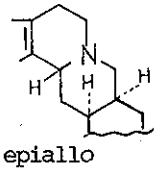
(59) a. normal



b. pseudo

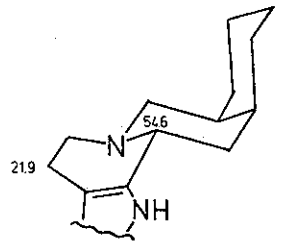


c. allo

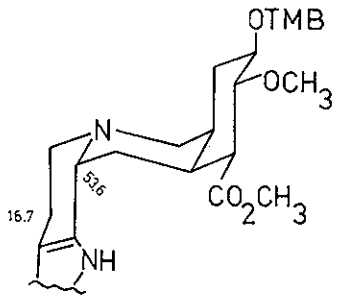


d. epiallo

(59d), the equilibrium between the trans- and the cis$_1$-conformation depends on the ring E substituents. Again δ(C3) and δ(C6) are diagnostic of the conformational state, as is shown for epialloyohimbane (60) and reserpine (61).

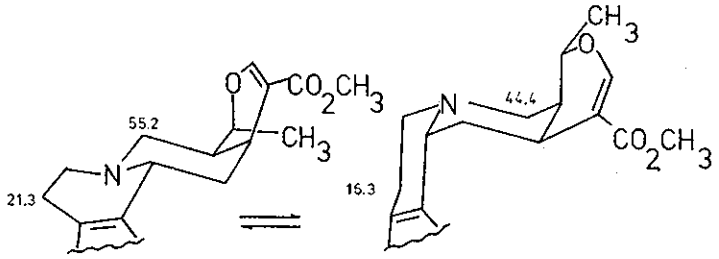


(60)



(61)

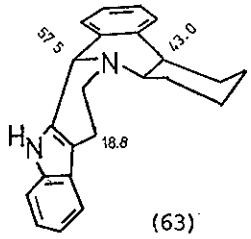
Intermediate values for these carbons, indicate a fast conformational equilibrium. This was shown in akwammigine (62), whose low temperature spectrum shows two sets of signals, corresponding to (62a) and (62b).



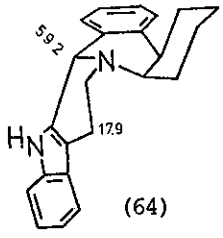
(62a) (62b)

With the use of these low temperature shifts an equilibrium constant of 1.3 ± 0.1 at 25° was obtained.

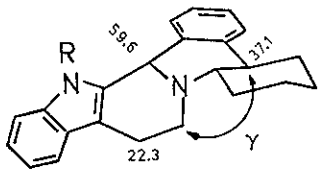
The characteristic chemical shift of the indole benzylic carbons of the tetrahydrocarboline unit was used to determine the quinolizideine conformation in compounds (63,64,65)[44]. The chemical shift of 22.3 ppm, along with the



(63)

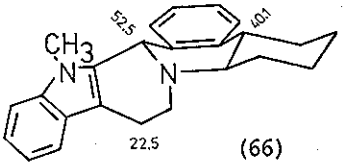


(64)



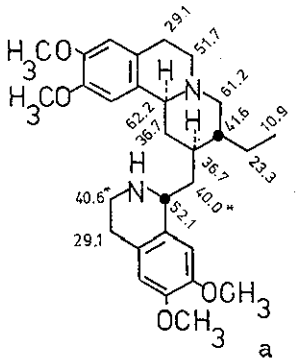
(65) a. R = H
b. R = CH_3

upfield shift of the γ-interacting carbons establish the cis_2 quinolizideine-conformation for (65), for which the ^{1}H NMR results had indicated a trans-form. N-methylation of (63) forces the molecule into conformation (66), in which one of the quinolizideine rings is a boat[36].

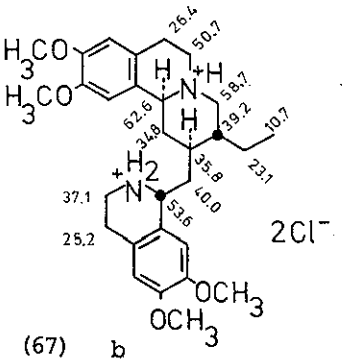


(66)

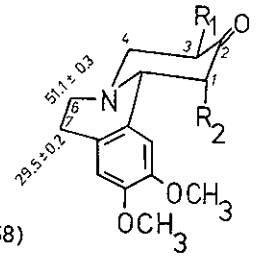
The same rules can be applied to determine the conformations of benzo-substituted quinolizidines, although the assignment of the benzylic carbon is somewhat more difficult by its occurrence at lower field. The spectrum of emetine (67a) was assigned by Wenkert[38], and the values for its dihydrochloride salt were also reported[45].



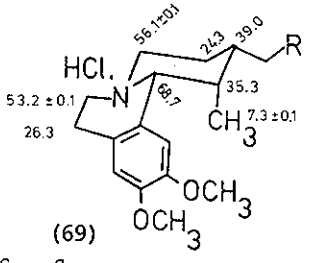
a



(67) b

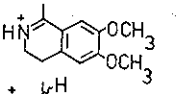


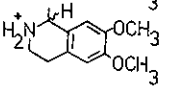
(68)

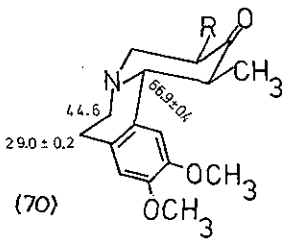


(69)

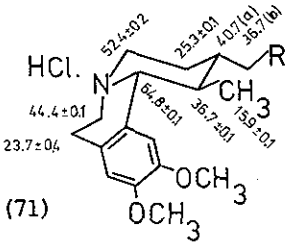
	δC_1	C_2	C_3	C_4	C_{11b}
a. $R_1 = R_2 = H$	47.6	208.5	41.1	54.7	61.5
b. $R_1 = H$, $R_2 = CH_3$	49.8	213.2	38.2	55.1	64.8
c. $R_1 = R_2 = CH_3$	49.6	214.6	40.9	63.2	65.6

a. R = 

b. R = 

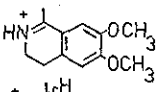


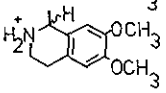
(70)



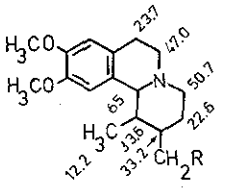
(71)

	δC_1	C_2	C_3	C_4
a. R = H	47.2	210.0	38.2	54.1
b. R = CH_3	46.4	211.2	40.8	62.7

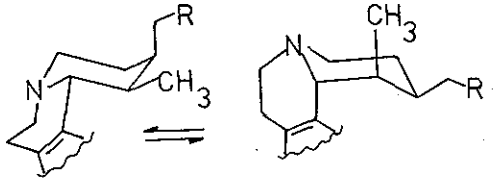
a. R = 

b. R = 

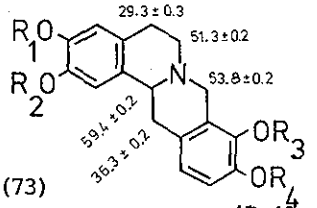
Several analogs of emetine (69,71,72) were also studied, with the aid of the chemical shifts of the trans-(68) and cis-(70)' quinolizideine derivatives. The intermediate chemical shifts of C6 (47.0 ppm) and of the CH_3 (12.2) in (72) probably indicate a conformational equilibrium between the two cis-conformers.



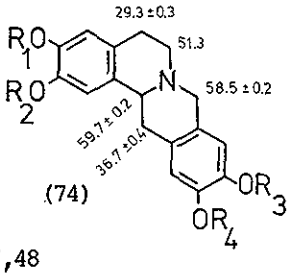
(72)



The spectra of a number of tetrahydroprotoberberines also show the characteristic shieldings on changing the quinolizideine conformation from trans (73,74) to cis (75), as shown on (76). Mainly δ(C6) is considered as the most diagnostic value by the authors[45].



(73)



(74)

a. $R_1 = R_2 = R_3 = R_4 = CH_3$ [47,48]

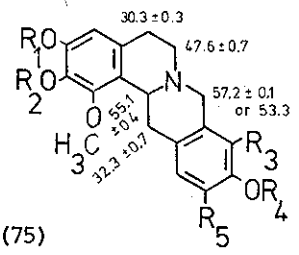
b. R_1-R_2 = $-CH_2-$, $R_3 = R_4 = CH_3$ [46,47,48]

c. R_1-R_2 = $-CH_2-$, R_3 = H, $R_4 = CH_3$ [46]

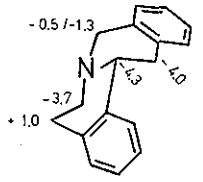
d. $R_1 = R_2 = R_4 = CH_3$, R_3 = H [47]

a. $R_1 = R_2 = R_3 = R_4 = CH_3$ [46]

b. R_1-R_2 = R_3-R_4 = $-CH_2-$ [46]



(75)



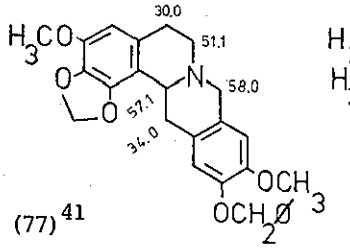
(76)

a. $R_1 = R_2 = R_4 = CH_3$, $R_3 = OCH_3$, $R_5 = H$[46]

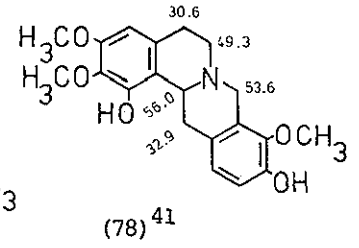
b. R_1-R_2 = $-CH_2-$, $R_3 = H$, $R_4 = CH_3$, $R_5 = OCH_2\phi$[46]

c. R_1-R_2 = $-CH_2-$, $R_3 = R_4 = R_5 = H$[46]

The chemical shifts of (77) indicate the trans-conformation for the 1,2-methylenedioxy-substituted compound, while the intermediate values for the 1-hydroxy compound (78) are interpreted as being averaged values due to a cis-trans equilibrium in this compound ; this has been proven independently by infrared spectroscopy[49]. The chemical shift of C8 can be used to detect a C-9 substitution[46], although methylation of a C-9 hydroxyl group does not affect δ(C8)[47].

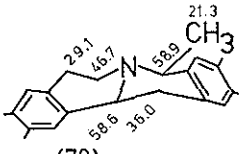


(77)[41]

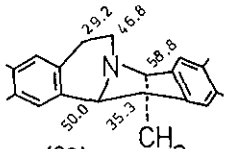


(78)[41]

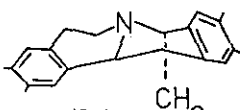
The two 8-methylsubstituted epimers, coralydine and O-methylcorytenchirine, have a trans (79) and a cis-quinolizideine (80) conformation respectively. The assignment of the cis-conformation for the latter, based on the high field position of C6, C13a and the methyl carbon[50], is however not very convincing, especially since no upfield shift of C13 is observed. These effects are also expected for the trans-conformation (81). The cis-conformation was nevertheless confirmed by the 270 MHz ^1H NMR spectra[51] and by X-ray analysis[52].



(79)

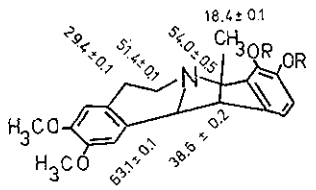


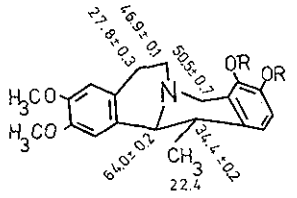
(80)



(81)

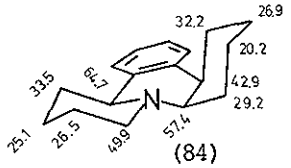
The diastereomeric 13-methyltetrahydroprotoberberines (82) and (83) were shown to have a trans- and a cis-quinolizideine conformation respectively[47].



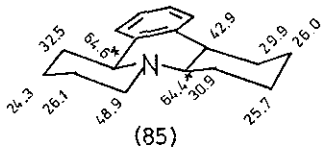


(82) a. R=CH_3 b. R-R=-CH_2- (83) a. R=CH_3 b. R-R=-CH_2-

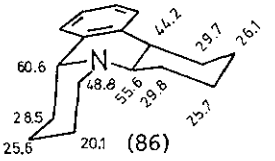
In these compounds, not only C6 and C13 are shifted upfield, but also C5 and C8. The small downfield shift of C13a in (83) may be explained by a change of the β effects of the methyl and C6-methylene. Thus, the effects of a cis-conformation resulting from C1 methoxysubstitution are different from those resulting from 13-methylsubstitution, which might be partly due to a somewhat different equilibrium constant in both series of compounds[49]. Nevertheless, the predominant conformation is easily deduced from the spectra. The ^{13}C spectra of the four isomers of 1,2,3,4,4a,6,7,8,9,13b-decahydro-9aH-pyrido[1,2-f]-phenanthridine (84-87)[11] confirmed their configuartion and the conformation as determined by ^{1}H NMR. In one isomer, the second component of the conformational equilibrium (87 ⇌ 88) could be identified as (88), mainly on the basis



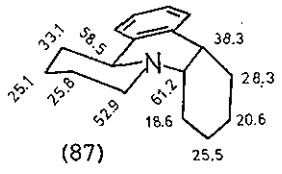
(84)



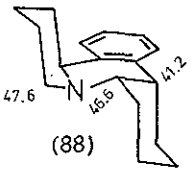
(85)



(86)

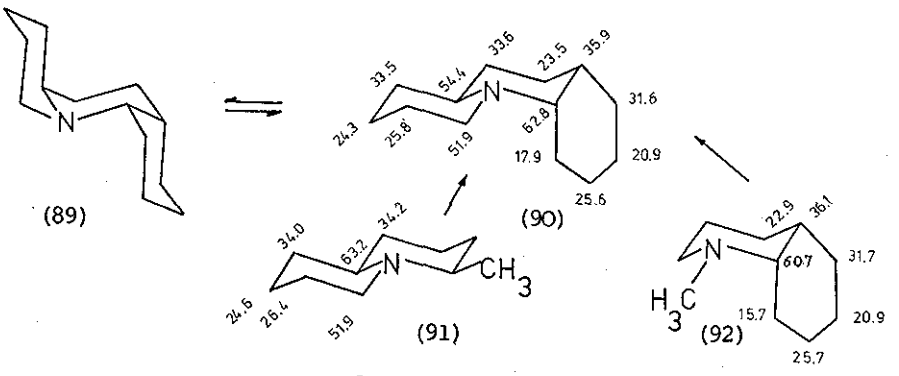


(87)



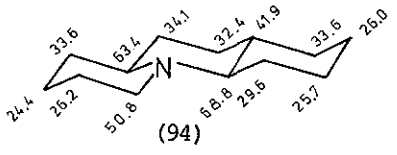
(88)

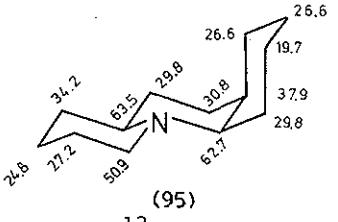
of the temperature dependence of the chem. shift values. Only three signals of the minor conformer (88) (2-3%) could be detected. The strong preference for the trans-cisoïd-cis conformation (87), is in contradiction with the reported cis-transoïd-cis conformation (89) for the analogous isomer of perhydrobenzo[c]quinolizidine. A comparison of the ^{13}C spectrum of this compound with the model compound (91) and (92) however clearly established its



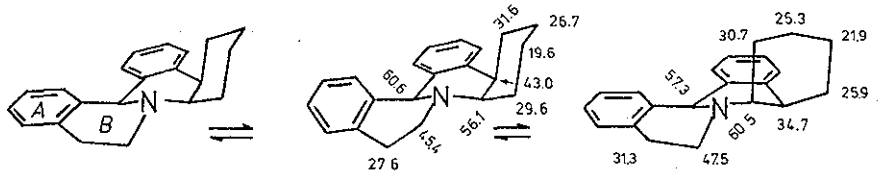
trans-cisoid-cis conformation (90)[16].

The reliability of these comparisons with model compounds was proven for two other isomers (94,95).

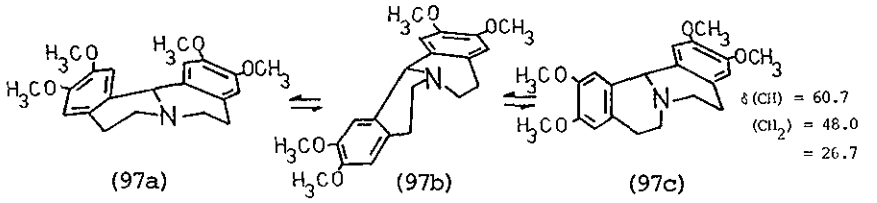




The possibility of observing the whole skeleton by ^{13}C NMR led to a reassignment of the conformational equilibrium in (96)[19]. The partial ^{1}H NMR analysis indicated an inversion of ring B, which was interpreted as an equilibrium between (96a ⇌ b). The low temperature carbon spectrum however showed an inversion of the D ring. The equilibrium is therefore between (96b) and (96c).



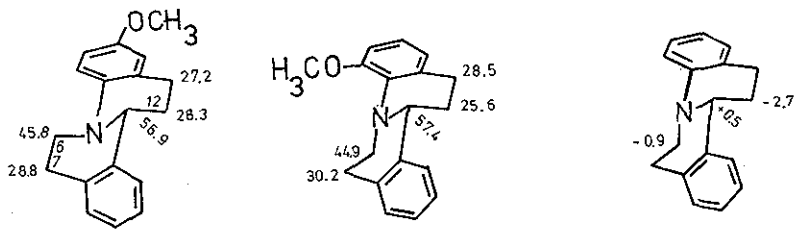
The conformation of dibenzo[a,h]quinolizidine was assumed to be trans (97a)[53]. The chemical shifts of the methylene carbons are however almost exactly the mean of those of the analogous carbons in (50) and (51), thus indicating a rapid equilibrium between two identical cis-conformations (97b ⇌ c)[36].



(97a) (97b) (97c)

An exception to the general rules has been observed for dibenzo[a,f]-substituted quinolizidines[54].

In these compounds, the delocalisation of the nitrogen lone pair over the aromatic ring in the trans-conformation (98) induces upfield shifts of the α-carbons. This delocalisation is not possible in the cis-compound (99). Only C12 therefore shows the expected upfield shift (100), comparable to those in (76).

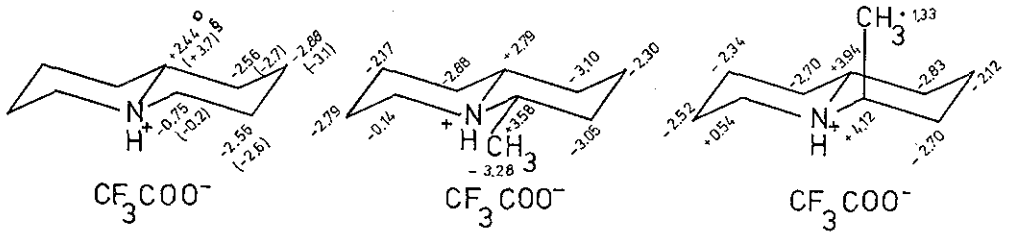


(98) (99) (100)
Δδ (99–98)

III. PROTONATION-, CONTACT-, QUATERNISATION- AND N-OXIDE SHIFTS

Protonation induced ^{13}C shifts are generally upfield for the β, γ and δ carbons. The C-H bond is electronically polarized more readily than the C-C bond by the inductive effect and therefore the C-H carbon has more electron density than the C-C carbon by protonation. This may explain the observed order of upfield shift of secondary carbon > tertiary carbon > quaternary carbon[23].

The effect of a positive charge on the α-carbons is dependent on its degree of substitution. These effects have been discussed in terms of linear electric-field shifts[55,56,68].

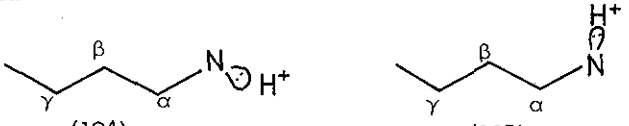


(101) (102) (103)

Fig 5 : Protonation shifts of quinolizidines

In quinolizidines (101-103), the α-methine carbons shift downfield, whereas the α-methylenes of (101) and (102) show upfield shifts.

In trifluoroacetic acid, a conformational dependance of the β-carbon shift was postulated by Morishima[23]. This was interpreted in terms of stereospecificity of the σ-inductive effect by a zigzag path (104) or a folded parth (105) mechanism.



(104) (105)

The β-carbons anti to the lone pair exhibit the largest protonation shifts.

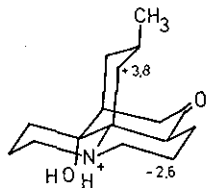
This mechanism is however questioned by Eliel[13]. A study of decahydroquinoline derivatives established that while the nature of the acid (HCl or CF_3COOH) has little effect on the shift differences upon protonation, there is a strong effect of solvent especially on the α and β carbons. In some cases shifts in opposing directions were observed for hydrochlorides in $CDCl_3$ and the trifluoroacetates in trifluoroacetic acid. The protonation shifts in chloroform solution did not show the conformational dependance, but are in the order $\alpha < \beta > \gamma < \delta$.

The opposite protonation shifts of the 4-methyl carbons in (102) and (103) is not explainable by a zigzag path mechanism for (103). The lowfield shift of the axial methyl in the latter, is due to a decrease of its shielding by

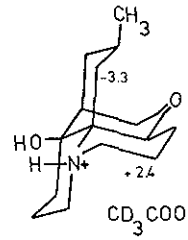
§ The values between brackets are for a solution in CF_3COOH.[23]
° $CDCl_3$ solution with excess CF_3COOH[15]

the β-anti lone pair[15] (see 14).

Titration experiments with CD_3COOD were done for lycopodium alkaloids[32], and the results were reported to agree with Morishima's results. The reason for the reversal of the protonation shift between epimers (106) and (107) is not clear.



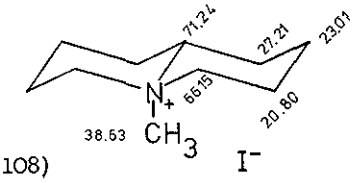
(106) CD_3COO^-



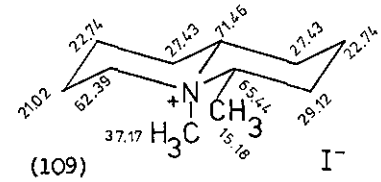
CD_3COO^- (107)

The zigzag and folded path mechanism was also used to explain $Ni(acac)_2$ induced contact shifts[57]. The largest shifts also occur at the β-carbon anti to the lone pair[57,58].

The ^{13}C spectra of the methiodides of substituted quinolizidines were measured[15,59,60]. The substituent parameters for an axial N-methyl group were estimated by subtracting the metiodide chemical shifts (e.g. (108) or (109)) from those of the protonated bases[15]. Those parameters show an analogous, though smaller, trend to those of the C-methyl substituent parameters.

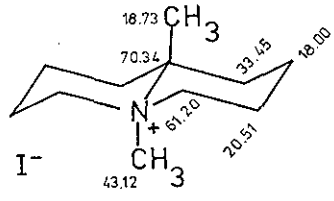


(108)

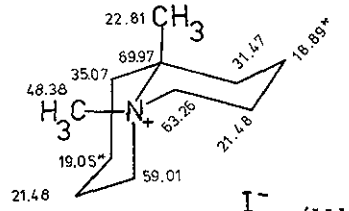


(109)

For angular 9a-substituted quinolizidine methiodides, the cis- and trans-methiodides are easily distinguished on the basis of the number of resonances. The N^+-CH_3 signal of cis-9a-substituted quinolizidine methiodides (e.g. 111) appears at lower field than those of the corresponding trans-methiodides[59,60] (e.g. 110).

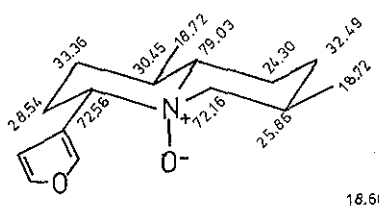


(110)

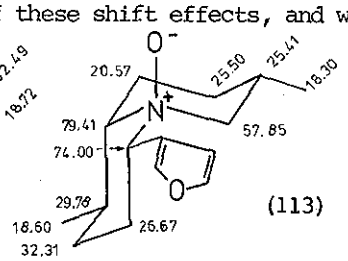


(111)

Changing a quinolizidine to a quinolizidine N-oxide, without changing the ringfusion, changes the chemical shifts of the carbons α, β and γ to the nitrogen by ca +10.53, -6.02 and +0.99 ppm respectively[27]. If N-oxidation is accompanied by a change to a cis-ringfusion, the γ-gauche interactions cause an upfield shift of the interacting carbons, although the deshielding effect of the positive nitrogen offsets these upfield shifts at the α and β carbons (e.g. 112, 113). With the aid of these shift effects, and with the

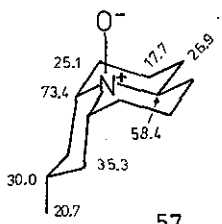


(112)

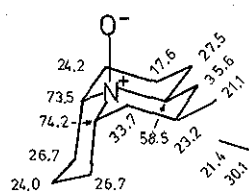


(113)

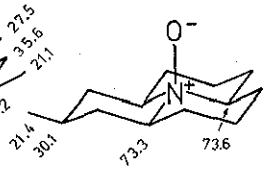
values of (35), the signals of the coccinellin alkaloids (114) and (115) can be assigned[61,62]. The chemical shifts of myrrhine N-oxide (116) have also been reported[63], but the assignment of the methylene carbons remains unclear.



(114)[57]



(115)[58]



(116)[59]

$\delta(CH_2)$ = 35.8 ppm
35.6
27.4
23.4

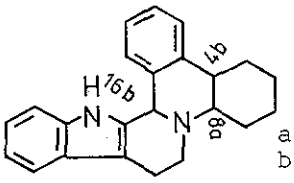
IV. SPIN-LATTICE RELAXATION TIMES

The relaxation rates ($1/T_1$) of the individual carbons of reserpine were used as a means to determine the number of directly attached protons[43], as an aid for the assignment of the resonances. Quaternary carbons can be distinguished by the influence of neighbouring protons on their T_1 values.

Indolo[2,3-a]quinolizidine (52) and its cis-2-tert-butyl derivative (54) have been shown to have a predominant ^{13}C-^{1}H-dipolar-dipolar relaxation mechanism for all carbons[10], and to undergo largely isotropic reorientation. The nonprotonated carbons are relaxed by the nearby protons, a fact of which can be used for assignment purposes.

V. $^1J(^{13}C-^1H)$

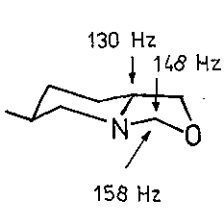
The nitrogen lone pair stereospecifically affects the one-bond C-H coupling constant of the adjacent carbon. The smaller value for an antiperiplanar vs a synclinal orientation has been used to determine the quinolizidine ring-fusion[41]. The relative small difference of 6-12 Hz requires an accurate determination of ^1J. A sufficient computer resolution should be available for the gated ^1H decoupled spectra. These usually show broad multiplets due to long range couplings. Reliable values have to be obtained by line shape simulations or by graphical determination of the gravity center of the multiplets[64]. A method for determining the difference in ^1J for a methylene carbon using the residual couplings in a series of off resonance decoupled spectra, or the width or height ratio of the central and outer peaks of a triplet has been described[65]. If possible, the determination of the carbon satellites in the proton spectrum gives the highest accuracy[64]. The discrepancy for the $^1J_{CH}$ value of (58a), the second value being consistent with the correct[44] stereochemistry, is due to these experimental difficulties. The values obtained for the hexahydro-3H-oxazolo[3,4-a]pyridines (117,118)[66], and



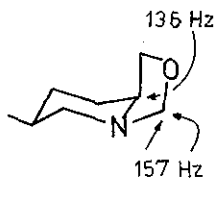
(63)	4b , 8a , 16b	^1J= 141 + 2Hz[a] 139 + 1Hz[b]
(64)	4b , 8a , 16b	= 140 ∓ 2Hz[a] 139 ∓ 1Hz[b]
(65)	4b , 8a , 16b	= 135 ∓ 2Hz[a] 137 ∓ 1Hz[b]

a. value directly read from the gated ^1H decoupled spectrum
b. value determined by the satellite method

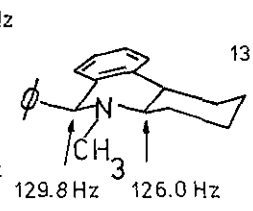
the octahydrophenanthridines (119, 120)[64] illustrate the potential of the method for determining the lone pair orientation; although the mechanism of



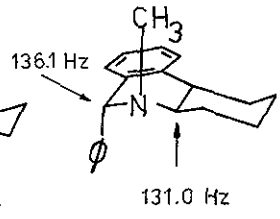
(117)



(118)

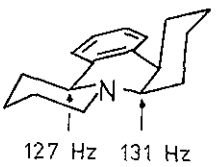


(119)

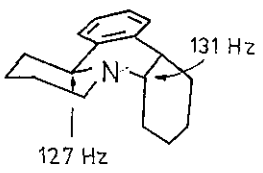


(120)

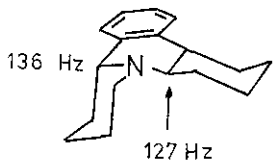
the stereospecific effect has been questioned in favour of a bond angle deformation effect[67]. The spread of the values in (121-125) however clearly indicate competing influences which remain to be studied.



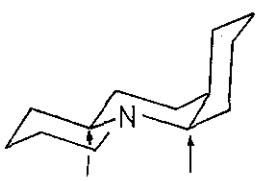
(121)

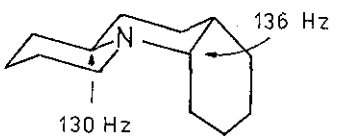


(122)



(123)





VI. ACKNOWLEDGEMENTS

We are indebted to the "Fonds voor Kollektief Fundamenteel Onderzoek" and the "Nationale Raad voor Wetenschapsbeleid" for their support.

VII. REFERENCES

1. Part XVI of the series Benzo- and Indoloquinolizidine Derivatives. For the preceding paper see ref. 54.

2. T.A. Crabb, R.F. Newton and D. Jackson, Chem. Rev. 71, 109 (1971).

3. T.A. Crabb, Annual Reports on NMR Spectroscopy, Vol. 6A, p 249, Academic Press, 1975.

4. N.K. Wilson and J.B. Stothers, in E.L. Eliel and N.L. Allinger (Eds.), Topics in Stereochemistry, Wiley-Interscience, New York, 1974, p. 1.

5. A.S. Perlin, in E. Buncel and C.C. Lee (Eds.), Isotopes in Organic Chemistry, Elsevier, Amsterdam, 1977, p 171.

6. E. Wenkert, C.J. Chang, D.W. Cochran and F.M. Schell, Acc. Chem. Res. 7, 46 (1974).

7. E. Wenkert, H.P.S. Chawla, C.-J. Chang, D.W. Cochran, E.W. Hagaman, J.C.King and K. Orito, J. Am. Chem. Soc. 98, 3645 (1976).

8. B.R. Pai, K. Nagarajan, H. Suguna and S. Natarajan, Heterocycles 6, 1377 (1977).

9. J.B. Lambert, D.A. Netzel, H. Sun and K.K. Lilianstrom, J. Am. Chem. Soc. 98, 3778 (1976).

10. G.W. Gribble, R.B. Nelson, J.L. Johnson and G.C. Levy, J. Org. Chem. 40, 3720 (1975).

11. G. Van Binst, G. Laus and D. Tourwé, Org. Magn. Res., in press.

12. D.K. Dalling, D.M. Grant and E.G. Paul, J. Am. Chem. Soc. 95, 3718 (1973).

13.a. E.L. Eliel and F.W. Vierhapper, J. Org. Chem. 41, 199 (1976).
b. F.W. Vierhapper and E.L. Eliel, J. Org. Chem. 42, 51 (1977).

14. G.J. Jordan and D.R. Crist, Org. Magn. Res. 9, 322 (1977).

15. M. Sugiura and Y. Sasaki, Chem. Pharm. Bull.22, 2988 (1976).

16. D. Tourwé, G. Laus and G. Van Binst, J. Org. Chem., in press.

17. S.F. Nelsen, G.R. Weisman, E.L. Clennan and V.E. Peacock, J. Am. Chem. Soc. 98, 6893 (1976).

18. E.L. Eliel, V.S. Rao, F.W. Vierhapper and G.Z. Juaristi, Tetrahedron Lett. 4339 (1976).

19. D. Tourwé, L. Vandersteen and G. Van Binst, Bull. Soc. Chem. Belg. 86, 603 (1977).

20. E.L. Eliel, W.F. Bailey, L.D. Kopp, R.L. Willer, D.M. Grant, R. Bertrand, K.A. Christensen, D.K. Dalling, D.W. Duch, E. Wenkert, F.M. Schell and D.W. Cochran, J. Am. Chem. Soc. 97, 322 (1975).

21. W. Kitching, M. Marriott, W. Adcock and D. Doddrell, J. Org. Chem. 41, 1671 (1976).
W. Adcock, B.D. Gupta and W. Kitching, J. Org. Chem. 41, 1498 (1976).

22. A.J. Jones, C.P. Beeman, A.F. Casy and K.M.J. Mc Erlane, Can. J. Chem. 51, 1790 (1973) ; see also ref 4, p 58.

23. I. Morishima, K. Yoshikawa, K. Okuda, T. Yonezawa and K. Goto, J. Am. Chem. Soc. 95, 165 (1973).

24. E. Wenkert, B. Chauncy, K.G. Dave, A.R. Jeffcoat, F.M. Shell and H.P.

Schenk, J. Am. Chem. Soc. 95, 8427 (1973).

25. R.T. LaLonde and T.N. Donvito, Can. J. Chem. 52, 3778 (1974).

26. H. Kessler, H. Möhrle and G. Zimmermann, J. Org. Chem. 42, 66 (1977). H. Kessler and G. Zimmermann, Chem. Ber. 110, 2306 (1977).

27. R.T. LaLonde, T.N. Donvito and A.I.-M. Tsai, Can. J. Chem. 53, 1714 (1975).

28. F. Bohlmann and R. Zeisberg, Chem. Ber. 108, 1043 (1975).

29. R.T. LaLonde and C.F. Wong, Can. J. Chem. 53, 3545 (1975).

30. R.T. LaLonde, C.F. Wong, A.I.-M. Tsai, J.T. Wróbel, J. Ruszkowska, K. Kabzinska, T.I. Martin and D.B. MacLean, Can. J. Chem. 54, 3860 (1976).

31. a. R.H. Mueller and R.M. DiPardo, J.C.S. Chem. Comm. 565 (1975). b. R.H. Mueller kindly provided us the chemical shift values.

32. T.T. Nakashima, P.P. Singer, L.M. Browne and W.A. Ayer, Can . J. Chem. 52 1936 (1975).

33. S.H. Grover and J.B. Stothers, Can. J. Chem. 52, 870 (1974). G. Engelhardt, H. Jancke and D. Zeigan, Org. Magn. Res. 8, 655 (1976).

34. The values between brackets refer to $\Delta\delta$(40-39). According to the authors[24], the γeffect of the axial carbomethoxy group on C-5 in (39) is exactly compensated by the γ-interaction with C-10a in (40). Since there is an additional γ-interaction with C-2, we preferred to revers the assignment of C-3 and C-5 in (40).

35. Nomenclature used by Wenkert[6].

36. D. Tourwé and G. Van Binst, unpublished results.

37. The first report of G.W. Gribble, R.B. Nelson, G.C. Levy and G.L. Nelson, J.C.S. Chem. Comm. 703 (1972) contains several reversed assignments.

38. M.C. Koch, M.M. Plat, N. Préaux, H.E. Gottlieb, E.W. Hagaman, F.M. Schell and E. Wenkert, J. Org. Chem. 40, 2836 (1975).

39. Previous studies of some of these compounds contain incorrect assignments[40-43].

40. R.H. Levin, J.-Y. Lallemand and J.D. Roberts, J. Org. Chem. 38, 1983(1973).

41. G. Van Binst and D. Tourwé, Heterocycles 1, 257 (1973).

42. T. Kametani, T. Higa, M. Ihara, K. Fukumoto and M. Kajiwara, J.Het. Chem. 12, 259 (1975).

43. F.W. Wehrli, Adv. Mol.Relax. Proc. 6, 139 (1974).

44. G. Van Binst, D. Tourwé and E. De Cock, Org. Magn. Res. 8, 618 (1976).

45. A. Buzas, R. Cavier, F. Cossais, J.P. Finet, J.P. Jacquet, G. Lavielle and N. Platzer, Helv. Chim. Acta 60, 2122 (1977).

46. T. Kametani, K. Fukumoto, M. Ihara, A. Ujüe and H. Koizumi, J. Org. Chem. 40, 3280 (1975).
T. Kametani, A. Ujüe, M. Ihara, K. Fukumoto and H. Koizumi, Heterocycles 3, 371 (1975).

47. D.W. Hughes, H.L. Holland and D.B. MacLean, Can. J. Chem. 54, 2252 (1976).

48. E. Wenkert, B.L. Buckwalter, I.R. Burfitt, M.F. Gasić , H.E. Gottlieb, E.W. Hagaman, F.M. Schell and P.P. Wovkulich, in G.C. Levy (Ed.), Topics in Carbon -13 NMR Spectroscopy, Vol. 2, Wiley-Interscience, New York 1976, p 81.

49. N. Takao and K. Iwasa, Chem. Pharm. Bull. 24, 3185 (1976).

50. T. Kametani, A. Ujüe, M. Thara and K. Fukumoto, J.C.S. Perkin I 1976,1218.

51. D. Tourwe, G. Van Binst and T. Kametani, Org. Magn. Res. 9, 341 (1977).

52. H. Bruderer, J. Metzger, A. Brossi and J.J. Daly, Helv. Chim. Acta 59, 2793 (1976).

53. D.C. Bishop and M.J. Tucker, J. Chem. Soc. C. 2184 (1970).

54. D. Tourwé, W. Van den Brandt and G. Van Binst, submitted for publication.

55. J.G. Batchelor, J. Am. Chem. Soc. 97, 3410 (1975).
J.G. Batchelor , J.C.S. Perkin II, 1585 (1976).

56. K. Seidman and G.E. Maciel, J. Am. Chem. Soc. 99, 3254 (1977).

57. K. Yoshikawa, K. Bekki, M. Karatsu, K. Toyoda, T. Kamio and I. Morishima, J. Am. Chem. Soc. 98, 3272 (1976).
I. Morishima and K. Yoshikawa, J. Am. Chem. Soc. 97, 2950 (1975).

58. K. Jankowski, J. Org. Chem. 41, 3321 (1976).

59. Y. Arata, T. Aoki, M. Hanaoka and M. Kamei, Chem. Pharm. Bull. 23, 333 (1975).

60. Y. Arata, M. Hanaoka and S.K. Kim, Chem. Pharm. Bull. 23, 1142 (1975).

61. B. Tursch, D. Daloze, M. Dupont, C. Hootele, M. Kaisin, J.M. Pasteels and D. Zimmermann, Chimia 25, 307 (1971).

62. D. Daloze, personnal communication.

63. W.A. Ayer, R. Dawe, R.A. Eisner and K. Furuichi, Can. J. Chem. 54, 473 (1976).

64. E. De Cock and G. Van Binst, unpublished results.

65. E.W. Hagaman, Org. Magn. Res. 8, 389 (1976).

66. Y. Takeuchi, P.J. Chivers and T.A. Crabb, J.C.S. Perkin II, 51 (1975).

67. D.G. Gorenstein, J. Am. Chem. Soc. 99, 2254 (1977).

68. J.G. Batchelor, J.Magn. Res. 28, 123 (1977).

Received, 26th December, 1977