BENZO- AND INDOLOQUINOLIZINE COMPOUNDS. IV.

THE USE OF ^{13}C-H COUPLING CONSTANTS IN THE STEREOCHEMICAL STUDY OF NITROGEN BRIDGEHEAD COMPOUNDS

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The preferential *cis* or *trans* quinolizidine conformation has been determined by measurement of the ^{13}C-H coupling constants of the C-H bonds next to the bridgehead nitrogen in benzo- and indoloquinolizidine compounds I - V.

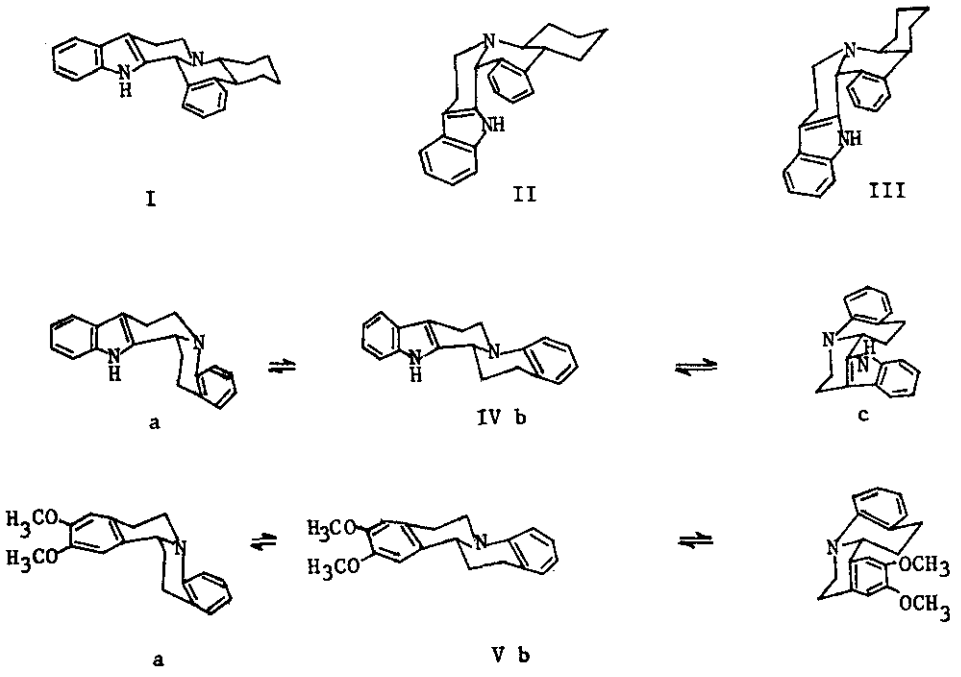
The most widely used spectroscopic methods for the determination of the conformation in quinolizine compounds are infrared and proton magnetic resonance spectroscopy[1]. The appearance of strong Bohlmann bonds in the ir spectrum is indicative of a *trans* quinolizidine conformation[2,3]. Ring distortion can cause these bands to disappear, although the *trans*-ring fusion is maintained[4].

In pmr spectroscopy, the shielding of the axial proton adjacent to an axial lone pair on nitrogen is used. This preferential shielding is observed in quinolizidine[5], decahydroquinolines[6,18], piperidines[7] and in a wide variety of compounds with bridgehead nitrogen atoms[8]. The conformation of benzo[a]- or indolo[2,3-a]quinolizines can be determined by the chemical shift of the angular C11b, resp. C12b proton[9]. The dividing line of δ = 3.8 ppm between a *cis*- and a *trans*-quinolizidine conformation is an approximation since long-range shielding effects have been reported to influence this position[10].

Trans-anti-N-methyl inside yohimbane which exists in a *cis*-quinolizidine conformation, shows a signal at δ = 3.65 ppm for the C-13b proton.

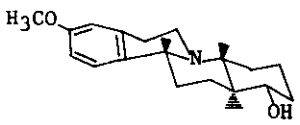
We have synthesized a number of benzo- and indoloquinolizine compounds I - V (Figure 1), for which the criterion of Uskokovic[9] is not valid due to the added benzene ring in the [f] or [h] position. In all these compounds the Bohlmann bands are absent (except a weak band at 1790 cm^{-1} for IV). This is not surprising in view of the strong interaction between the aromatic rings in the *trans*-quinolizidine conformation (see I).

Figure 1



The absence of Bohlmann bands in the 18-Nor-D-*homo*-8-azasteroid VI (Figure 2), a compound very similar to IV and V, has been noted[4].

Figure 2



VI

The conformation of compounds I and II could be determined by the differential shielding of axial *versus* equatorial protons and by their protonation shifts[11]. This protonation shift ($\Delta\delta CF_3COOH - \delta CHCl_3$) for H16b in compound III is 0.62 ppm, which means a *cis*-quinolizidine ring fusion[11]. For compounds IV and V this protonation shift value (0.81 and 0.73 ppm) allows no conclusion about the preferential quinolizidine conformation.

Several authors have reported on the stereospecific effect of the nitrogen lone pair on the $^{13}C_\alpha$-H coupling constant[12]. This effect is ascribed to partial delocalization of the lone pair electrons into the antiparallel CH bond[12,13]. As a result the $^1J(^{13}CH)$ for a *cis* configuration of the proton and the lone pair is 6-12 Hz[12,14] larger than for the *trans* orientation.

We investigated the use of this stereochemical relationship in the quinolizidine compounds. The coupling constants were obtained from the alternatively decoupled ^{13}C spectra[15] and are collected in Table I.

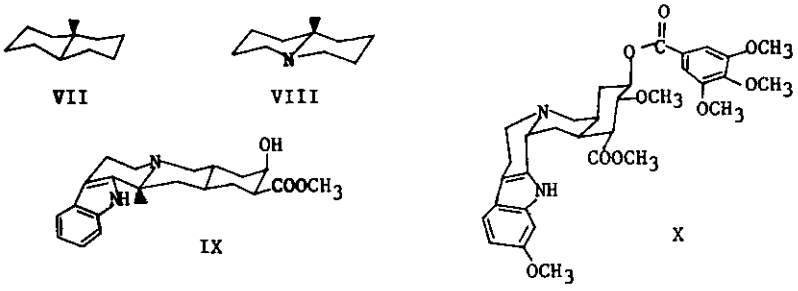
Table I : ^{13}C - H Coupling Constants Hz

Compound	$^1J(^{13}CH)$ of angular CH	$^1J(^{13}CH)$ of C8a - H	$^1J(^{13}CH)$ of C4b - H
I	135 ± 2	135 ± 2	123 ± 2
II	141 ± 2	136 ± 2	126 ± 2
III	140 ± 2	135 ± 2	127 ± 2
IV	136 ± 2		
V	133 ± 3*		
VII	125 ± 2		
VIII	123 ± 2		
IX	133 ± 2		
X	139-142 ± 2		
XI	141 ± 2		

*The larger error is due to partial overlap of the doublet with the methoxy quadruplets.

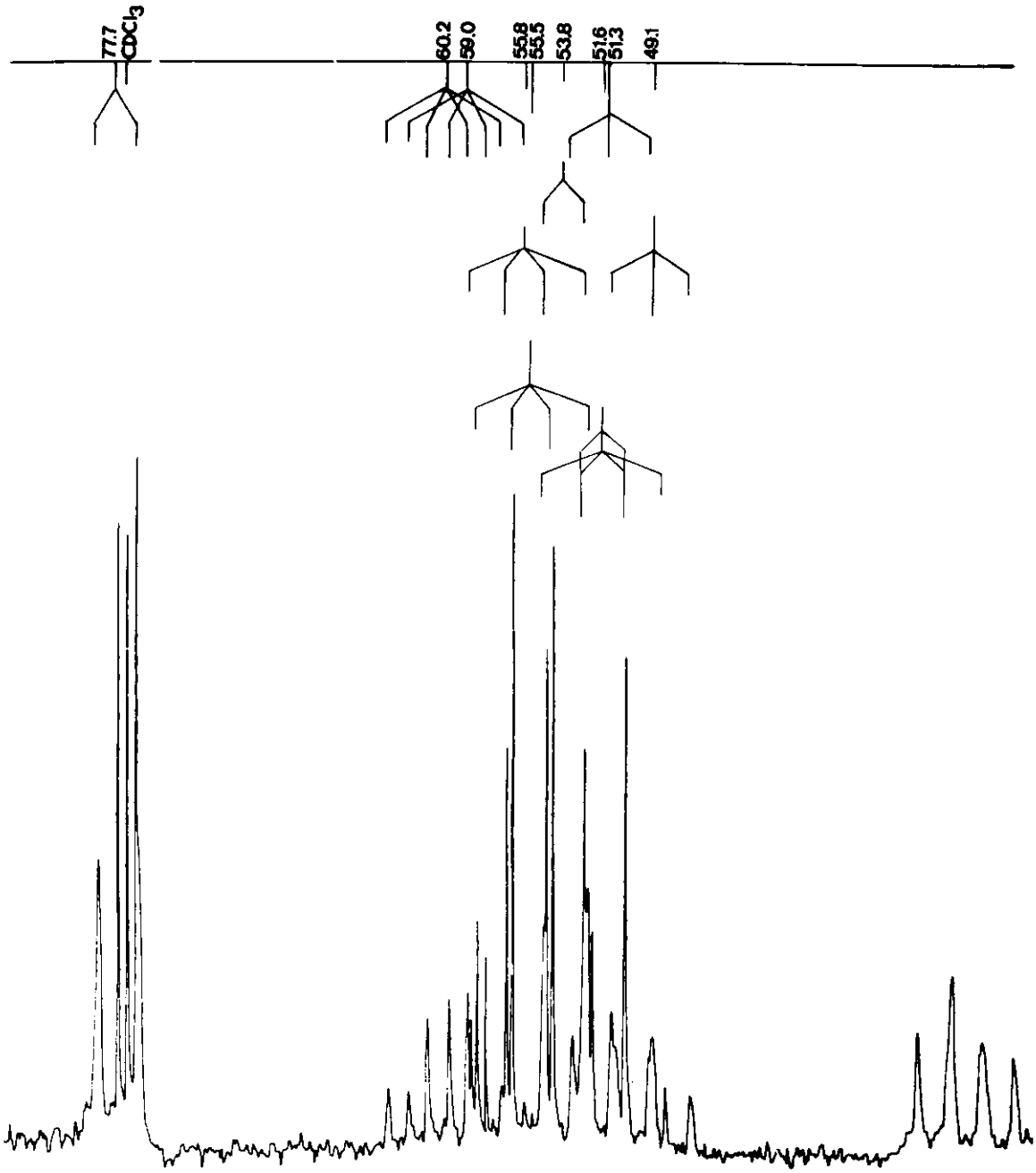
We first investigated the $^1J(^{13}CH)$ in some model compounds VII - X (Figure 3), to check the applicability to our compounds I - V.

Figure 3



The very low $^1J(^{13}CH)$ = 123 Hz in quinolizidine VIII compared with $^1J(^{13}CH)$ = 125 Hz in *trans* decaline VII is in agreement with the *trans* orientation of the nitrogen lone pair and the C9a - H bond[1]. It is indeed expected that the introduction of the nitrogen atom would increase $^1J(^{13}CH)$ due to its electronegativity. The hyperconjugation effect reduces the coupling back to a smaller value.

The cmr spectrum of yohimbine IX was analyzed by Roberts and his coworkers,[16] who attributed the signal at δ_{TMS} = 60.4 ppm to C-3. This signal shows a $^1J(^{13}CH)$ = 133 ± 2 Hz. These authors also assigned the resonances of reserpine X. The signal at δ_{TMS} = 61.0 ppm, which was attributed to C-3[16], however showed a quadruplet in the alternatively decoupled spectrum, whereas the signal at δ = 54.0 ppm showed a doublet instead of the reported triplet. The peak at δ = 51.9 ppm, which represents three carbons at 15.09 MHz, was resolved in our spectrometer, operating at 67.88 MHz. These signals at δ= 51.9, 51.7 and 51.3 ppm show a quadruplet, doublet and triplet multiplicity. For these reasons, we assigned the lowest field doublet to C-3. The C-H coupling constant could not be measured in the undecoupled spectrum due to overlapping lines. By adding a small amount (10-20 weight %) of $Pr(fod)_3$ or $Eu(fod)_3$, a minimum value of 139 - 142 Hz was determined.



Alternatively decoupled cmr spectrum of reserpine X (500 mg) shifted with 70 mg Pr(fod)3. Only region between 80 and 32 ppm is shown. Shifts relative to the unshifted spectrum are : 77.7 ppm (- 0.5 and - 1.3), 60.2 (- 0.7), 59.0 (- 1.7), 55.8 (0.0), 55.5 (- 0.8), 53.8 (- 0.2), 51.6 (- 0.3 and - 0.1), 51.3 (0.0), 49.1 (0.0).

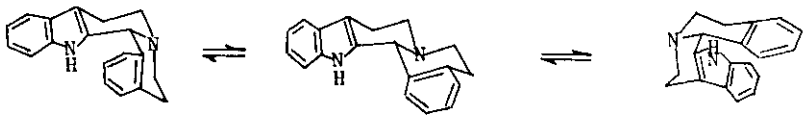
According to J.D. Roberts[16], the shift reagent preferentially complexes with the trimethoxybenzoyl group. It is therefore assumed that this complexation will not have a significant effect on the nitrogen lone pair, and thus on the C-3 coupling constant.

The difference between a *cis*-quinolizidine (reserpine IX) and a *trans*-quinolizidine (yohimbine VIII) amounts to 6 - 9 Hz. From Table 1, it is apparent that the preferential quinolizidine conformation in compounds I, II and III is reflected into the $^1J(^{13}CH)$ and that all three compounds have the same orientation of C8a - H towards the nitrogen lone pair. As a proof that the observed effect is associated with the lone pair orientation, the $^1J(^{13}CH)$ of compounds I and II were determined in CF_3COOH, where the lone pair is protonated. Both compounds show about the same coupling constant for C16b - H : 142 ± 1 Hz and 143 ± 1 Hz (note 1). The unchanged coupling constant of C4b - H also supports this view.

The low values of the coupling constants in IV and V also point to a preferential *trans*-quinolizidine conformation IVb and Vb.

By this method the *cis*-conformation of the hexahydrobenz[h]indolo[2,3-a]-quinolizine compound XI is evident (Figure 4).

Figure 4



a XI b c

A choice between conformation XIa and XIc however is not possible by this method.

Note 1 : We thank Mr. M. Alla and Mr. E. Lippmaa (Institute of Cybernetics of the Estonian Academy of Sciences, Tallinn, USSR) for the measurements of these coupling constants by their H - {^{13}C} double resonance technique[17].

From the extensive line broadening of all carbon resonances except C14b in the cmr spectrum at - 70 °C, it seems that the compound is rapidly interconverting between the two *cis*-conformations XIa and XIc.

The stereochemical dependance of $^{1}J(^{13}CH)$ can also be used in the conformational analysis of decahydroquinolines. The small coupling constant of C8a - H in *cis*- and *trans*-decahydroquinoline XII and XIII (Figure 5, Table 2) is in agreement with the conclusion of H. Booth[18] about the preferential conformation XIIb in the *cis*-isomer. It also allows the conclusion that in the *trans* isomer, the NH has a preferential equatorial position (XIIIa).

Figure 5

XIIa XIIb XIIIa XIIIb

Table 2

Compound	Carbon	$J(^{13}CH)$ (25°)
XII	8a	128.5
XIII	8a	127.0
	4a	129.0

Although the method of directly reading the coupling constants from the spectra introduces a relatively large experimental error, it seems that the method can be used in cases where the classical ir and pmr methods fail to give results.

The application to the assignment of the stereochemistry in the dibenzo-[a,c]- and tribenzo[a,c,h]quinolizidine series will be published lateron.

The spectra were taken on a Bruker HDX-270 superconducting magnet, in 10 mm O.D. tubes. The concentrations varied from 200 mg to 300 mg (500 mg for reserpine) in 2.5 ml $CDCl_3$, also used for deuterium stabilization. The pulsinterferograms were accumulated in a Nicolet 1085 computer (20 k) and Fourier transformed. The pulse width for the broad band ^1H decoupled spectra was 10 µsec (± 15 °C), with a puls repetition time of 0.4 sec.

For the alternatively decoupled spectra, puls width was 20 µsec (± 30°). The decoupling pulselength was 0.8 to 1 sec with a total delay for the f_1 pulse of 1 to 1.2 sec. The spectra were taken with a sweep width of 7042.3 Hz and 3000 to 16000 scans were accumulated. All the angular carbons were located in the cmr spectra by selective decoupling of the appropriate carbon resonances in compounds I - III.

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