CONFORMATIONAL STUDIES OF 1- AND 3-ETHYL-1,2,3,4,6,7,12,12b-OCTAHYDROINDOLO[2,3-a]QUINOLIZINES

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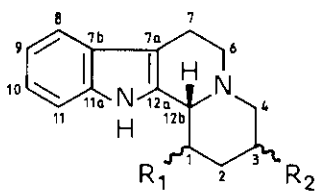
Abstract - A mainly ^{13}C NMR based conformational study of the 1- and 3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines 1-4 is presented.

In connection with synthetic studies on therapeutically valuable vincamine and pseudovincamine derivatives we became interested in 1- and 3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines 1-4* as potential model compounds. It turned out that although the four compounds have been described before in some details,[1,2] a mainly ^{13}C NMR based conformational study of them was highly desirable.



1 $R_1 = \beta$,-CH_2-CH_3; R_2 = H
2 $R_1 = \alpha$,-CH_2-CH_3; R_2 = H
3 R_1 = H ; $R_2 = \alpha$,-CH_2-CH_3
4 R_1 = H ; $R_2 = \beta$,-CH_2-CH_3

*Only one enantiomeric form is presented in the formulae for the compounds, which are, of course, racemic.

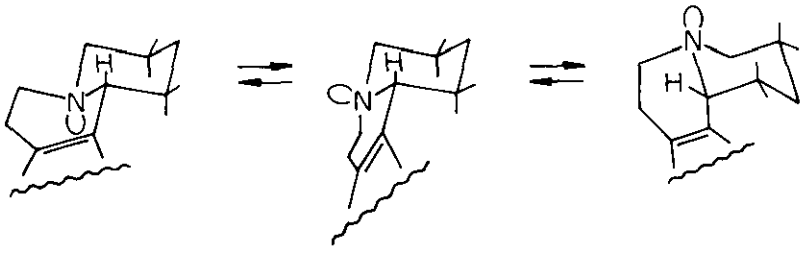
The four ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines 1-4:

Alkylation of 3-ethylpyridine with tryptophyl bromide[3] yielded the corresponding pyridinium salt. Catalytic hydrogenation of the salt furnished the N-tryptophyl-ethylpiperidine, whose indole N was protected by the acid labile t-butyloxy-carbonyl (Boc) group. The corresponding N-oxide was subjected to the modified Polonovski reaction[4] conditions and the intermediate iminium salts were reacted with KCN to give the corresponding α-aminonitriles. Treatment of the mixture of α-aminonitriles with $AgBF_4$, and then HCl/MeOH, yielded the indolo[2,3-a]quinolizines 1[5] and 3[6] which were separated by preparative TLC. Wolff-Kishner reduction of the earlier described 1-acetylindolo[2,3-a]quinolizine (Ref. 7, compound 8) afforded 1-ethylindolo[2,3-a]quinolizines 1[5] and 2[8] (due to a partial epimerization at C(1) before the reduction), which were separated by preparative TLC.

The ^{13}C NMR data of the "missing" ethylindolo[2,3-a]quinolizine (compound 4) have been described recently in the literature.[9] The data presented here for compound 4[10] are taken from Refs. 1 and 9.

Conformational considerations:

The 1- or 3-substituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine systems can exist in six conformations (two configurations) with equilibration by nitrogen inversion and cis-decalin type ring interconversion (Scheme 1). Ring C is assumed to be in the half chair conformation and only the chair forms of ring D are considered.



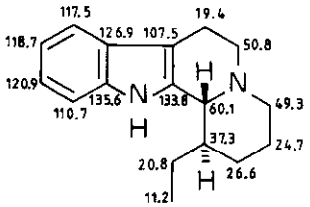
a b c

Compound 2 (to avoid steric interactions between an equatorial ethyl group and the indolic part) and compound 4 (to have an equatorial ethyl group) can be expected to exist predominantly in the trans-fused C/D ring conformation (conformer a) whereas for compound 1 (to avoid steric interactions between an equatorial ethyl group and the indolic part) and compound 3 (to have an equatorial ethyl group) the contribution of conformer c to the conformational equilibrium should be more pronounced.

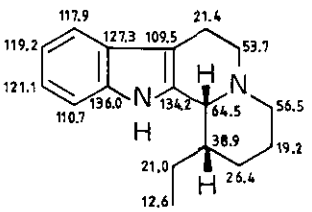
Stereochemical results:

The stereochemical relationship proposed for 1-4 were mainly determined by ^{13}C NMR spectral analysis. The fully proton-decoupled spectra, taken in $CDCl_3$, showed the chemical shifts depicted on the formulae. The proper shift assignment was confirmed by recording single frequency, off-resonance decoupled (sford) spectra and through reference to the earlier shift assignment.[11,13]

A general comparison of the chemical shifts found for compounds 1-4 with those of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (Ref. 11, compound 5a), taking into account the conformational considerations (vide supra) and the shielding effects of the ethyl groups, gives clear evidence of the stereostructures depicted in the formulae 1-4.



1



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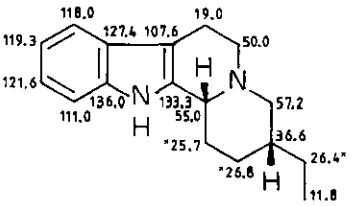

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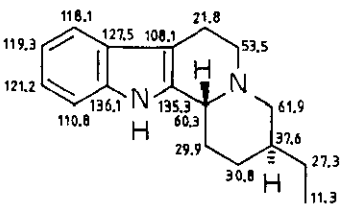
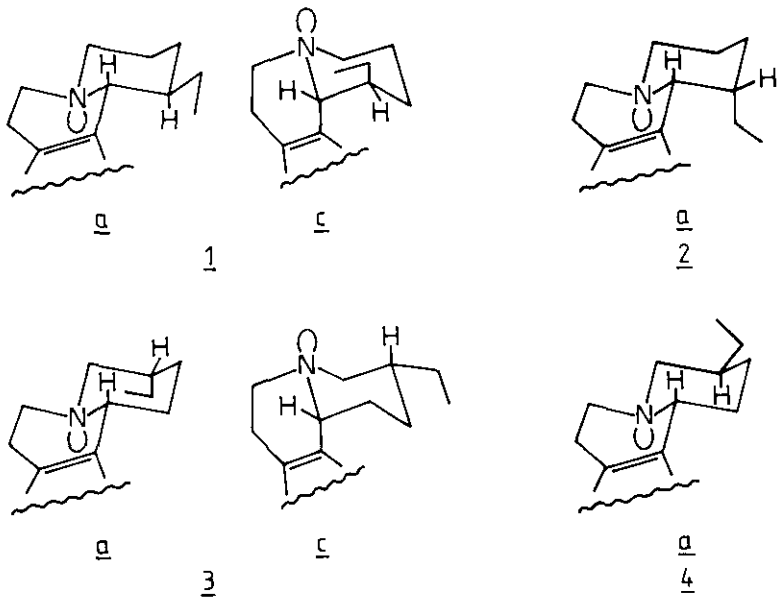


4

The chemical shift of C(7) reflects the contribution of different conformations to the conformational equilibrium (mainly due to the involvement of C(7) with C(4)). Taking the shift values (δ 21.8 and 16.8 ppm) as a basis[12], the present conformational equilibrium between conformers a and c (the contribution of conformer b is considered negligible) can be estimated with a relatively high degree of accuracy. Correlation of the shift values 19.4 and 19,0 ppm, found for the signal of C(7) in compounds 1 and 3, with the values 21.8 and 16.8 ppm indicates that the contribution of conformer c to the conformational equilibrium between a and c is about 48% and 56%, respectively. The values 21.4 and 21.8 ppm found for C(7) of compounds 2 and 4 underline the strong preponderance of conformation a.



a c a

1 2

a c a

3 4

The predominance of conformation a in compounds 2 and 4 is also supported by ^{1}H NMR spectroscopy. The presence of the C(12b)H signal upfield from δ 3.4 ppm (δ 3.34 and 3.20 ppm, respectively) is characteristic of conformation a (trans-quinolizine juncture). The coupling constant J = 2 Hz found for the C(12b)H signal of 2 is in excellent agreement with the proposed structure taking into account the conformational considerations (vide supra).

Owing to the diamagnetic displacement effect of the electron pair of the basic nitrogen (cf. conformational considerations), the C(12b)H signals of 1 and 3 appear at lower field (δ 3.69 and 3.90 ppm, respectively), in agreement with the proposed structures.

Moreover, the relatively strong intensities of the Bohlmann bands in the IR spectra of compounds 2 and 4 and their weakness in the IR spectra of compounds 1 and 3 are in full agreement with the conformational conclusions presented.

The present results put the stereochemistry of the four possible 1- and 3-ethyl-indolo[2,3-a]quinolizines 1-4 on a firm basis and give valuable data for stereochemical considerations of synthetic vincamine and pseudovincamine intermediates.

REFERENCES AND NOTES

1. E. Wenkert and B. Wickberg, J. Am. Chem. Soc., 84, 4914 (1962).
2. J.-Y. Laronze, J. Laronze, B. Caron, J. Lévy and J. Le Men, Bull. Soc. Chim. France, 1977, 1207.
3. T. Hoshino and K. Shimodaira, Justus Liebigs Ann. Chem., 520, 19 (1935).
4. M. Lounasmaa and A. Koskinen, Heterocycles, 22, 1591 (1984).
5. 1: ir 2820 (vw), 2750 (vw), pmr 0.98 (3H, t, J = 7.2 Hz, $-CH_2-\underline{CH_3}$), 3.69 (1H, J = 5 Hz, H-12b), 7.10-7.54 (4H, m, arom. H), 8.40 (1H, br s, NH), m/z 254 (M^+), 253 (100%), 239, 225, 170, 169.
6. 3: ir 2820 (vw), 2750 (vw), pmr 0.96 (3H, t, J = 7.2 Hz, $-CH_2-\underline{CH_3}$), 3.90 (1H, m, H-12b), 7.00-7.55 (4H, m, arom. H), 8.30 (1H, br s, NH), m/z 254 (M^+), 253 (100%), 239, 225, 170, 169.
7. M. Lounasmaa and M. Puhakka, Acta Chem. Scand., B 32, 216 (1978).
8. 2: ir 2830 (m), 2770 (m), pmr 0.80 (3H, t, J = 7.2 Hz, $-CH_2-\underline{CH_3}$), 3.34 (1H, d, J = 2 Hz, H-12b), 7.00-7.53 (4H, m, arom. H), 7.73 (1H, br s, NH), m/z 254 (M^+), 253 (100%), 239, 225, 170, 169.
9. G. Massiot, F. Sousa Oliveira and J. Lévy, Bull. Soc. Chim. France II, 1982, 185.
10. 4: ir 2810 (m), 2760 (m), pmr 0.95 (3H, t, $CH_2-\underline{CH_3}$), 3.20 (1H, m, H-12b), 7.00-7.55 (4H, m, arom. H), 7.70 (1H, s, NH), m/z 254 (M^+), 253 (100%), 205 (=225?), 170, 169.
11. M. Lounasmaa and R. Jokela, Tetrahedron, 34, 1841 (1978).
12. The values 21.8 and 16.8 ppm are found[13] for the signals of C(7) in the two possible 2-t-butyl-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]-quinolizines (compounds 2 and 3 in Ref. 13) where the C(2) t-butyl group, with its overwhelming equatorial preference is used to force the compounds to exist essentially only in one conformation (conformation a or c). It is assumed, that the values 21.8 and 16.8 ppm represent relatively well also the chemical shifts of C(7) for pure conformations a and c of ethylindolo-[2,3-a]-quinolizines 1-4.
13. G.W. Gribble, R.B. Nelson, J.L. Johnson and G.C. Levy, J. Org. Chem., 40, 3720 (1975).

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