EFFECT OF C-1, C-2, AND C-3 SUBSTITUENTS ON THE CONFORMATIONAL EQUILIBRIUM OF INDOLO[2,3-*a*]QUINOLIZIDINES

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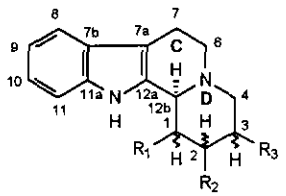
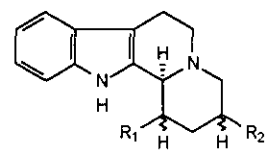
Abstract - Conformational behavior of indolo[2,3-*a*]quinolizidines possessing alkyl (or similar) and/or methoxycarbonyl substituents at C-1, C-2, and/or C-3 positions has been examined. Effects influencing the conformational equilibrium are discussed. A method of predicting the predominant conformation, usually with good accuracy, is described. Combined with ^{13}C NMR data the method can be used for stereochemical conclusions.

In connection with our work on indole alkaloids[1-3] of indolo[2,3-*a*]quinolizidine type, we became interested in their conformational behavior. We have earlier examined[4] the factors affecting the conformational equilibrium between the C and D rings of geissoschizine isomers and their model compounds possessing either *E*- or *Z*-ethylidene side chain at C-3 (IUPAC numbering; corresponding to C-20 in the biogenetic numbering).[5] In the present work we examine the effects of alkyl (in some cases 2'-alkoxycarbonylethyl) and methoxycarbonyl substituents at C-1, C-2, and C-3 (IUPAC numbering; corresponding to C-14, C-15, and C-20, respectively, in the biogenetic numbering)[5] on the conformational equilibrium between the C and D rings (*à titre d'exemples*: compounds **1** - **4**).[6]

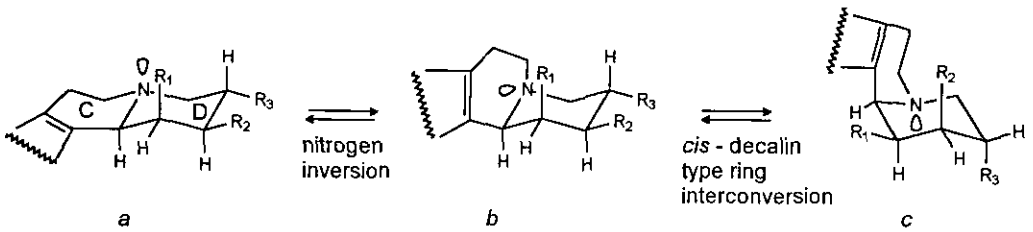




1 R_1 = H or Et, R_2 = H or R, R_3 = H or Et
2 R_1 = H or Et, R_2 = H or R, R_3 = H or Et

3 R_1 = H or Et, R_2 = H or CO_2Me
4 R_1 = H or CO_2Me, R_2 = H or Et

Owing to nitrogen inversion and *cis*-decalin-type ring interconversion (ring D in chair conformation), the indolo[2,3-*a*]quinolizidine skeleton can exist in three main conformations (conformations *a*, *b*, and *c*, Scheme 1).[1-3] The existence of ring D in boat and twist-boat conformations, in addition to the normal chair conformation, also has to be taken into consideration.



Scheme 1. Conformational equilibrium of indolo[2,3-*a*]quinolizidines.

It is noteworthy that the D ring substituents which in conformations *a* and *b* are axial become equatorial in conformation *c*, and *vice versa*.

In regard to the conformational behavior of compounds of the present type (*vide infra*), three general factors should be taken into consideration:

1°. The stability of conformation *a per se* is higher than that of conformation *c* [~11 kJ/mol (~2.6 kcal/mol)].[7] The role of conformation *b* is generally transitory and its contribution to the conformational equilibrium is generally small (except in the N_a-Boc protected compounds).[8] The contribution of different conformations to the conformational equilibrium is strongly influenced by the substituents.

2°. The C-1, C-2, and C-3 substituents generally prefer an equatorial position, although their reciprocal interactions may complicate the situation (*vide infra*). As a first approximation, the conformation where as many substituents as possible occupy an equatorial position can be considered the preponderant one. However, notice must be taken of the A-values of different substituents.[9,10]

3°. Interactions (by hydrogen bond formation) of substituents possessing appropriate hydroxyl or similar group with N_a or N_b may play a role (Figure 1). As this is not the case for the compounds considered here, the question is not threated further in this review. Readers interested in the question should consult our previous article.[4]

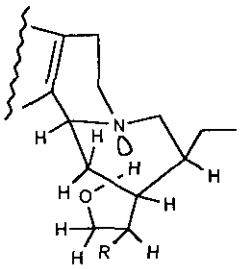


Figure 1. Example of hydrogen bonding between the C-2 substituent ($-CH_2CH_2OH$) and N_b (*conformation c*, ring D in boat conformation).

There are also at least two additional factors which may strongly influence the conformational equilibrium and need to be taken into consideration. In the present review we particularly focus our attention on these supplementary factors.

4°. There is a strong interaction between the axial C-1 and C-3 substituents (1,3-diaxial interaction).[11]

5°. A relatively strong steric interaction exists between equatorial alkyl (and similar) substituents at C-1 and the indolic part of the molecule, especially in conformation *a*. It is noteworthy that equatorial methoxycarbonyl substituents do not exhibit the same phenomenon in appreciable amount.

The ^{13}C NMR shift values of compound (**5**)[12] (Figure 2) were used as base values in the conformational analysis. As indicated by the characteristic signals at δ 60.3 (C-12b), 53.5 (C-6), and 21.6 (C-7) compound (**5**) exists preponderantly (>95%) in conformation *a*. [Note! In order to compensate for the small contribution (<5%) of conformation *c* to the conformational equilibrium, the C-7 value δ 21.6 ppm is replaced by δ 22.0 ppm in the calculations (*vide infra*)].

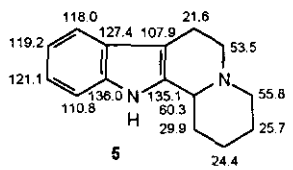


Figure 2. Measured ^{13}C NMR shift values of compound (**5**).[12]

The estimated shift values given in Figure 3 are taken to represent with relatively good accuracy the shift values of compound (**5**) when it is totally in conformation *c*. The values are based on those measured for

the *trans*-2-*tert*-butyl analogue of compound (5), which is estimated to exist ≥99.9% in conformation *c*, and on the assumption that a *tert*-butyl group noticeably affects only the directly attached carbon (C-2).[13,14]

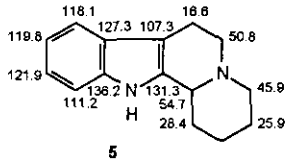


Figure 3. Estimated ^{13}C NMR shift values for conformation *c* of compound (5).

Although several other characteristic signals (*e.g.* those of C-12b and C-4) were used as a basis for the first approximation of the contribution of conformations *a* and *c* to the conformational equilibrium, for simplicity we refer in the discussion and calculations that follow only to the C-7 values δ 22.0 ppm (corrected value; *vide supra*) and δ 16.6 ppm.

1β-Ethylindolo[2,3-*a*]quinolizidine (6)

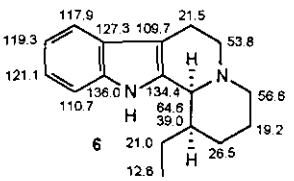
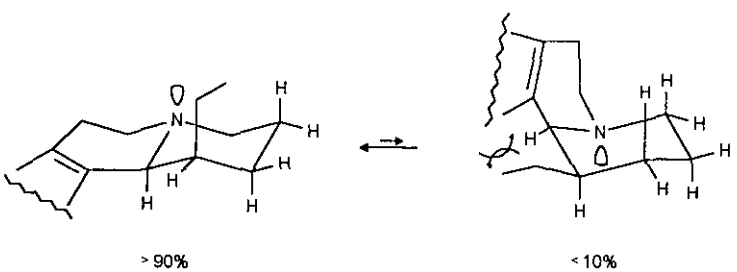


Figure 4. Measured ^{13}C NMR shift values of compound (6).[13]

Compound (6)[13,15] exists preponderantly (>90%) in conformation *a* (C-7 δ 21.5 ppm) with ring D in chair conformation. This permits the C-1 substituent to be in axial position (this time the energetically more favorable position) and to avoid interaction with the indolic part of the molecule, as in conformation *c* (Scheme 2).



Scheme 2. Conformational equilibrium of compound (6).

1α-Ethylindolo[2,3-*a*]quinolizidine (7)

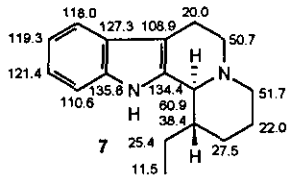
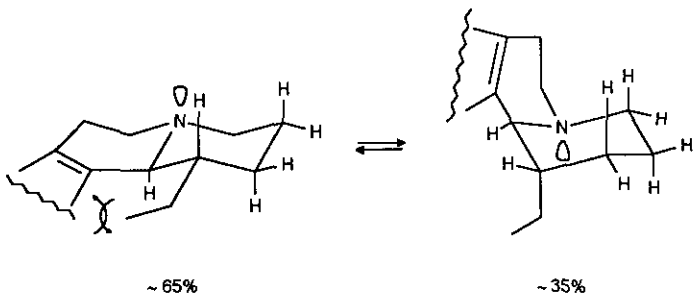


Figure 5. Measured ^{13}C NMR shift values of compound (**7**).[13]

Comparison of the measured shift value δ 20.0 ppm of compound (**7**)[13,15] with the values δ 22.0 ppm and δ 16.6 ppm indicates that the contributions of conformers *a* and *c* to the conformational equilibrium are about 65% and 35%, respectively. In conformation *a*, where the C-1 substituent is equatorial, there is interaction between the C-1 substituent and the indolic part of the molecule (Scheme 3).



Scheme 3. Conformational equilibrium of compound (7).

2β-Ethylindolo[2,3-*a*]quinolizidine (8)

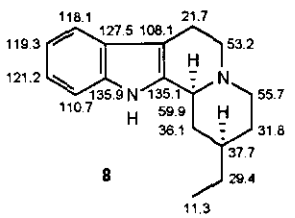
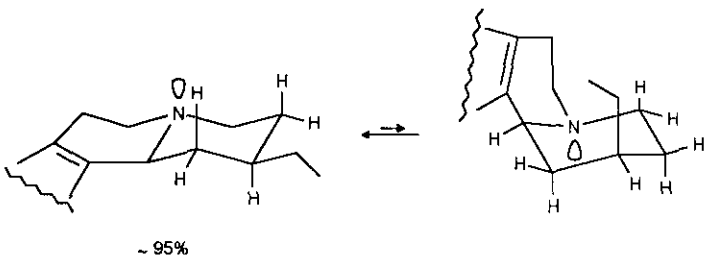


Figure 6. Measured ^{13}C NMR shift values of compound (**8**).[13]

Compound (**8**)[13] exists mostly (~95%) in conformation *a* (C-7 δ 21.7 ppm) and the C-2 substituent in equatorial position (Scheme 4).



Scheme 4. Conformational equilibrium of compound (**8**).

2α-Ethylindolo[2,3-*a*]quinolizidine (9)

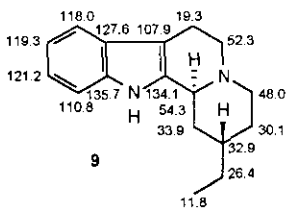
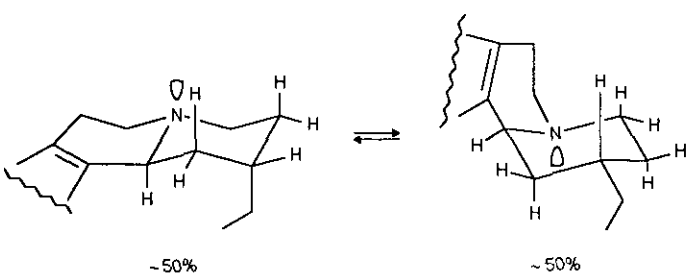


Figure 7. Measured ^{13}C NMR shift values of compound (**9**).[13]

Comparison of the measured shift value δ 19.3 ppm of compound (**9**)[13] with the values δ 22.0 ppm and δ 16.6 ppm indicates that the contributions of conformers *a* and *c* to the conformational equilibrium are about 50% and 50%. In conformation *c* the C-2 substituent assumes the energetically more favorable equatorial position, which partly compensates for the fact that conformation *c per se* is less favorable than conformation *a* (Scheme 5).



Scheme 5. Conformational equilibrium of compound (**9**).

2β-Malonylindolo[2,3-*a*]quinolizidine (10)

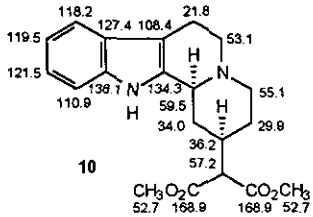
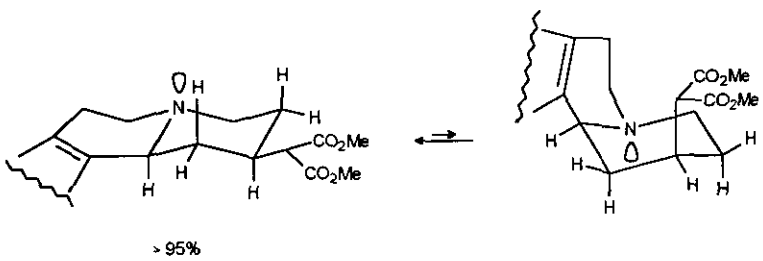


Figure 8. Measured ^{13}C NMR shift values of compound (**10**).[16]

Compound (**10**)[16,17] exists mostly (>95%) in conformation *a* (C-7 δ 21.8 ppm). This permits the bulky C-2 substituent to occupy the energetically more favorable equatorial position (Scheme 6).



Scheme 6. Conformational equilibrium of compound (**10**).

2α-Malonylindolo[2,3-*a*]quinolizidine (11)

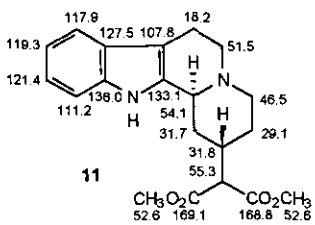
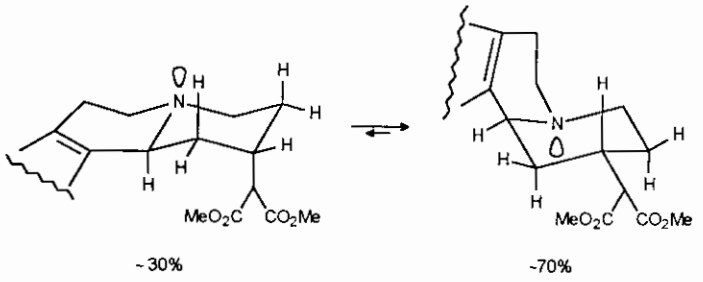


Figure 9. Measured ^{13}C NMR shift values of compound (**11**) (*the original assignments given*[16] for C-4 and C-6 are interchanged).

Comparison of the measured[16,17] shift value δ 18.2 ppm of compound (**11**) with the values δ 22.0 ppm

and δ 16.6 ppm indicates that the contributions of conformers *a* and *c* to the conformational equilibrium are about 30% and 70%, respectively. In conformation *c* the bulky C-2 substituent assumes the energetically more favorable equatorial position (Scheme 7).



Scheme 7. Conformational equilibrium of compound (**11**).

3α-Ethylindolo[2,3-*a*]quinolizidine (12)

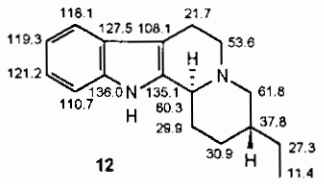
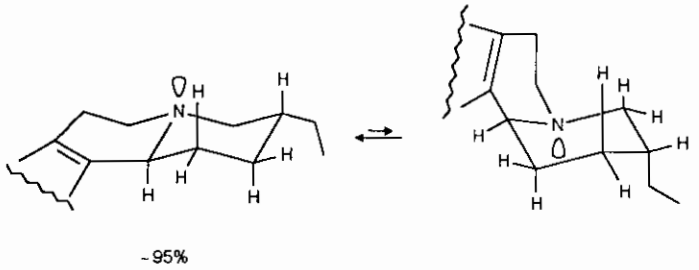


Figure 10. Measured ^{13}C NMR shift values of compound (**12**).[13]

Compound (**12**)[13,15,18] exists mostly (~95%) in conformation *a* (C-7 δ 21.7 ppm). The C-3 ethyl substituent is in equatorial position (Scheme 8).



Scheme 8. Conformational equilibrium of compound (**12**).

3β-Ethylindolo[2,3-*a*]quinolizidine (13)

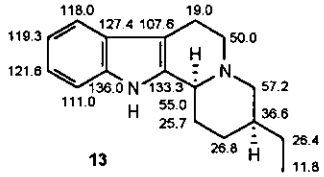
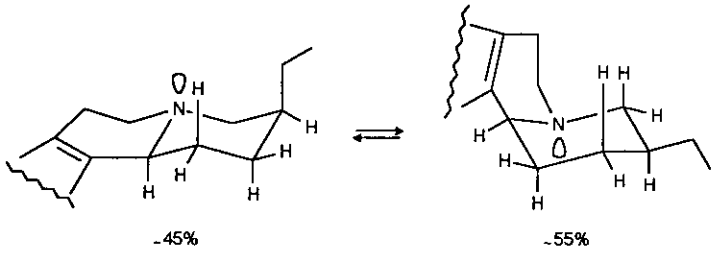


Figure 11. Measured ^{13}C NMR shift values of compound (**13**).[13]

Comparison of the measured[13,15,18] shift value δ 19.0 ppm of compound (**13**) with the values δ 22.0 ppm and δ 16.6 ppm indicates that the contributions of conformers *a* and *c* to the conformational equilibrium are about 45% and 55%, respectively. In conformation *c* the C-3 ethyl substituent occupies the energetically more favorable equatorial position (Scheme 9).



Scheme 9. Conformational equilibrium of compound (**13**).

1α-Methoxycarbonylindolo[2,3-*a*]quinolizidine (14)

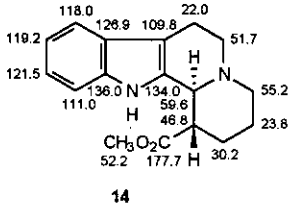
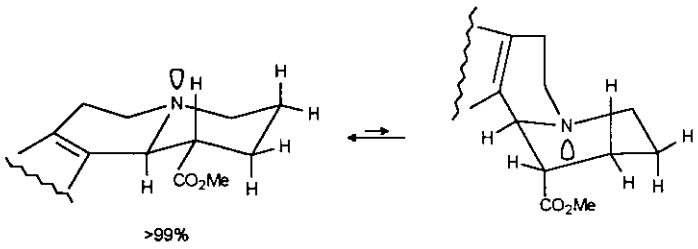


Figure 12. Measured ^{13}C NMR shift values of compound (**14**).[19]

Compound (**14**)[12,19] exists practically totally (>99%) in conformation *a* (C-7 δ 22.0 ppm)(Scheme 10). In contrast to an ethyl group (*vide infra*), the interaction between an equatorial methoxycarbonyl group and the indolic part of the molecule is not energetically unfavorable (*e.g.* hydrogen bonding possibility).



Scheme 10. Conformational equilibrium of compound (**14**).

1β-Methoxycarbonylindolo[2,3-*a*]quinolizidine (15)

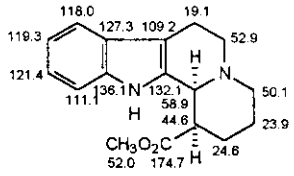
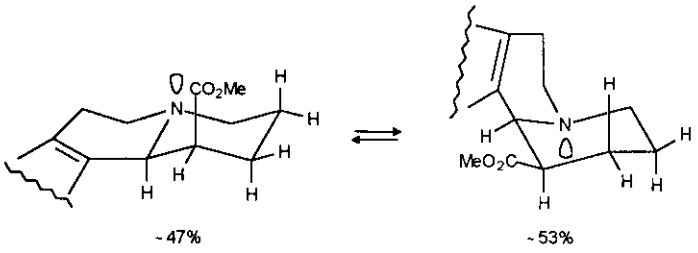


Figure 13. Measured ^{13}C NMR shift values of compound (**15**).[19]

The shift value δ 19.1 ppm given[19] for C-7 of compound (**15**) indicates that the contribution of conformers *a* and *c* to the conformational equilibrium is about fifty-fifty (~47% and ~53%) (Scheme 11).



Scheme 11. Conformational equilibrium of compound (**15**).

3β-Methoxycarbonylindolo[2,3-*a*]quinolizidine (16)

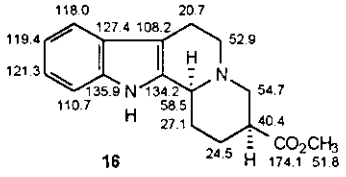
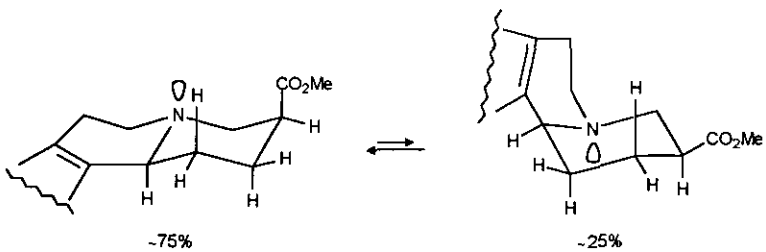


Figure 14. Measured ^{13}C NMR shift values of compound (**16**).[8]

Comparison of the measured[8] shift value δ 20.7 ppm of compound (**16**) with the values δ 22.0 ppm and δ 16.6 ppm indicates that the contributions of conformers *a* and *c* to the conformational equilibrium are about 75% and 25%, respectively. Thus conformation *a* predominates despite an axial C-3 substituent (Scheme 12).



Scheme 12. Conformational equilibrium of compound (**16**).

3α-Methoxycarbonylindolo[2,3-*a*]quinolizidine (17)

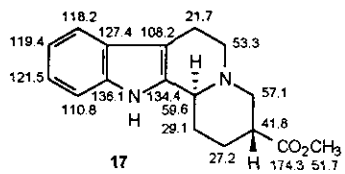
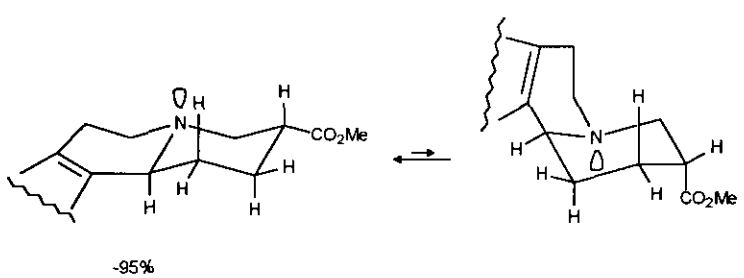


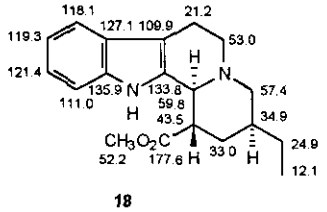
Figure 15. Measured ^{13}C NMR shift values of compound (**17**).[8]

Compound (**17**)[8] exists mostly (~95%) in conformation *a* (C-7 δ 21.7 ppm). This permits the C-3 substituent to occupy the equatorial position (Scheme 13).



Scheme 13. Conformational equilibrium of compound (17).

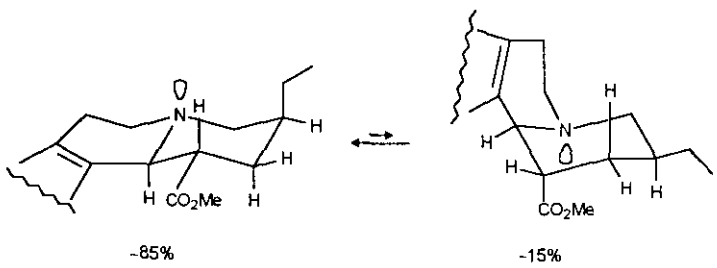
1α-Methoxycarbonyl-3β-ethylindolo[2,3-*a*]quinolizidine (18)



18

Figure 16. Measured ^{13}C NMR shift values of compound (**18**).[20]

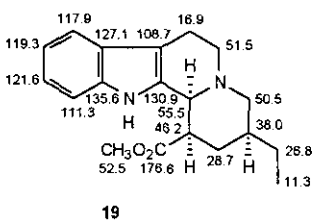
Comparison of the measured[20] shift value δ 21.2 ppm (C-7) of compound (**18**) with the values δ 22.0 ppm and δ 16.6 ppm indicates that the contributions of conformers *a* and *c* to the conformational equilibrium are about 85% and 15%, respectively (Scheme 14).



~85% ~15%

Scheme 14. Conformational equilibrium of compound (**18**).

1β-Methoxycarbonyl-3β-ethylindolo[2,3-*a*]quinolizidine (19)

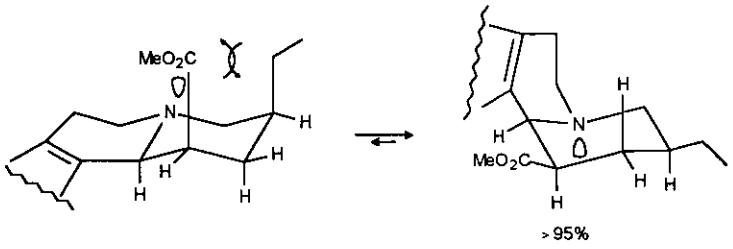


19

Figure 17. Measured ^{13}C NMR shift values of compound (**19**).[21]

Compound (**19**)[21] exists nearly totally (>95%) in conformation *c* (C-7 δ 16.9 ppm). In conformation *a* both substituents are in the axial positions which are energetically less favorable *per se*, and there is a strong

reciprocal interaction (diaxial 1,3-interaction) between the C-1 methoxycarbonyl group and the C-3 ethyl group (Scheme 15). In conformation *c* both substituents lie in the energetically more favorable equatorial positions. We emphasize that an equatorial C-1 methoxycarbonyl group is not energetically unfavorable.



Scheme 15. Conformational equilibrium of compound (**19**).

1α-Methoxycarbonyl-3α-ethylindolo[2,3-*a*]quinolizidine (20)

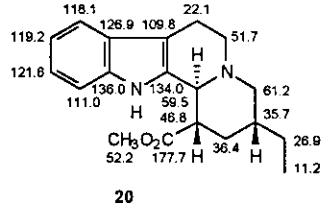
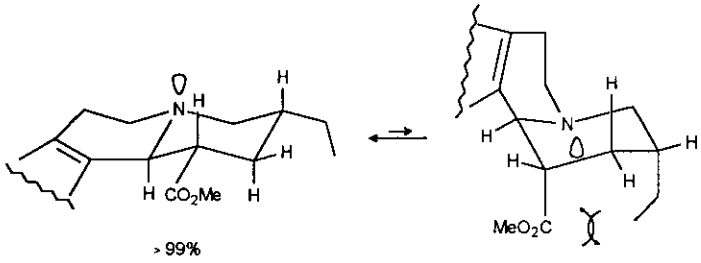


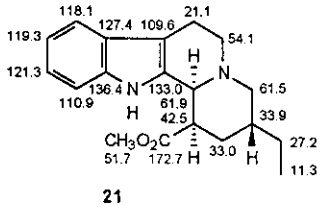
Figure 18. Measured ^{13}C NMR shift values of compound (**20**).[22]

Compound (**20**)[22] exists virtually entirely (>99%) in conformation *a* (C-7 δ 22.1 ppm). In conformation *c* both substituents are in axial positions, which are energetically less favorable *per se*. Moreover, there is a strong reciprocal interaction (diaxial 1,3-interaction) between the substituents (Scheme 16).



Scheme 16. Conformational equilibrium of compound (**20**).

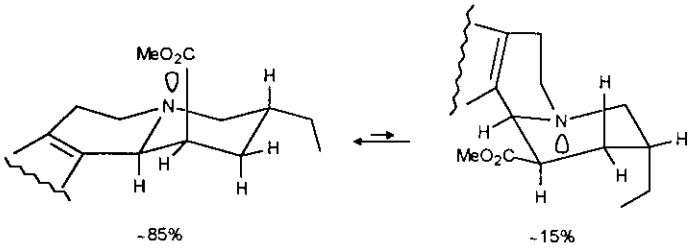
1β-Methoxycarbonyl-3α-ethylindolo[2,3-*a*]quinolizidine (21)



21

Figure 19. Measured ^{13}C NMR shift values of compound (**21**).[22]

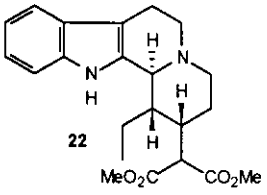
Comparison of the measured[22] shift value δ 21.1 ppm (C-7) of compound (**21**) with the values δ 22.0 ppm and δ 16.6 ppm shows that the contributions of conformers *a* and *c* to the conformational equilibrium to be about 85% and 15%, respectively (Scheme 17).



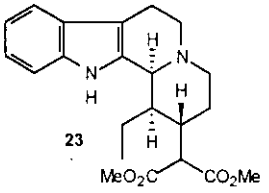
Scheme 17. Conformational equilibrium of compound (**21**).

APPLICATIONS

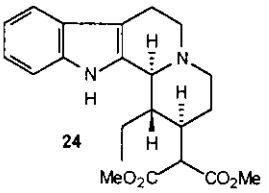
In connection with their work on indole alkaloid syntheses, Husson and coll.[16] prepared three "inside" indoloquinolizidine derivatives: **22** [compound (**29**) in Ref. 16], **23** [compound (**31**) in Ref. 16], and **24** [compound (**30**) in Ref. 16].



22



23



24

As these compounds seemed interesting for the present study we reexamined their ^{13}C NMR data (*vide infra*).

1α-Ethyl-2α-malonylindolo[2,3-*a*]quinolizidine (22)

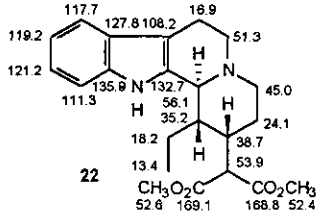
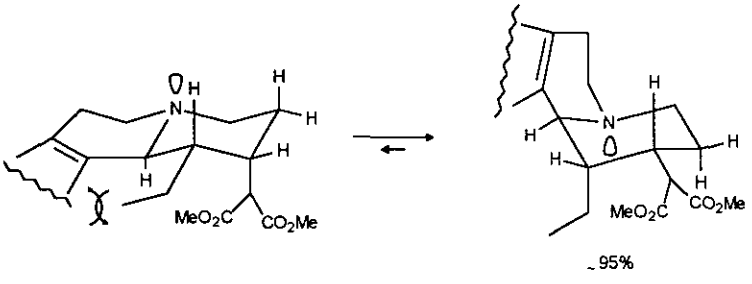


Figure 20. Measured ^{13}C NMR shift values of compound (**22**)(original assignments given for C-4 and C-6 *are interchanged*).[16]

Compound (**22**)[16] could be expected to exist mostly (~95%) in conformation *c*, and this is confirmed by the measured shift value C-7 δ 16.9 ppm. The C-1 ethyl substituent is in axial position to avoid interaction with the indolic part of the molecule and the bulky C-2 substituent in the energetically more favorable equatorial position (Scheme 18). The spectral data are in agreement with the proposed stereostructure.



Scheme 18. Conformational equilibrium of compound (**22**).

1α-Ethyl-2β-malonylindolo[2,3-*a*]quinolizidine (23)

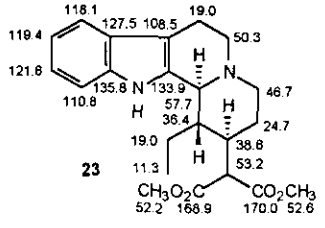
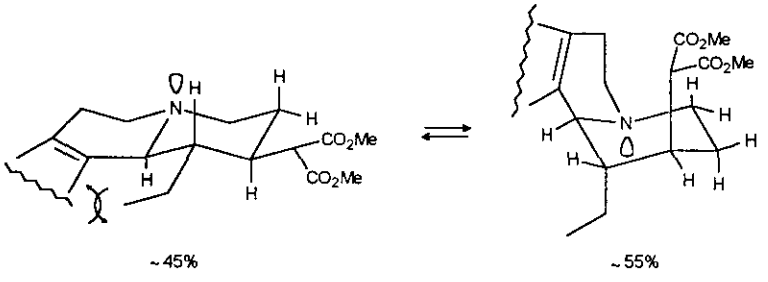


Figure 21. Measured ^{13}C NMR shift values of compound (**23**).[16]

Contributions of conformers *a* and *c* to the conformational equilibrium of compound (**23**)[16] could be expected to be nearly the same. Strong interaction between the equatorial C-1 ethyl substituent and the indolic part of the molecule in conformation *a* favors the contribution of conformation *c* even though the fact that the bulky C-2 substituent becomes axial (Scheme 19). Comparison of the measured shift value δ 19.0 ppm with the values δ 22.0 ppm and 16.6 ppm indicates that the contributions of conformer *a* and *c* are about 45% and 55%, respectively. This is in good agreement with the proposed stereostructure.



Scheme 19. Conformational equilibrium of compound (**23**).

1-Ethyl-2-malonylindolo[2,3-*a*]quinolizidine (24) (stereostructure 24a *versus* 24b)

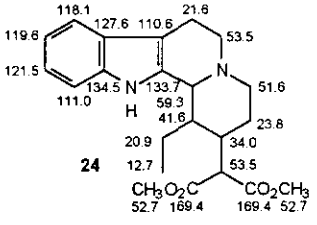


Figure 22. Measured ^{13}C NMR shift values of compound (**24**).[16]

1β-Ethyl-2α-malonylindolo[2,3-*a*]quinolizidine (24a) (earlier proposed[16] stereostructure)

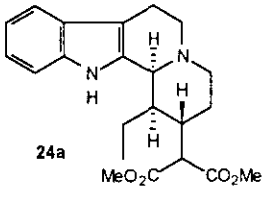
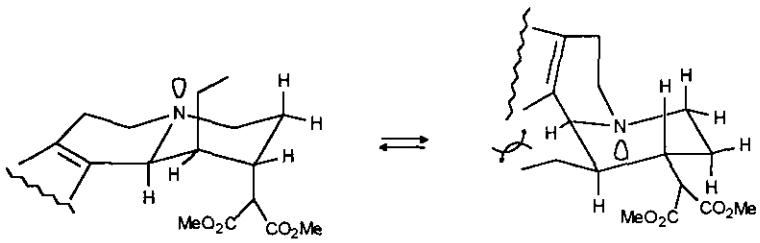


Figure 23. Stereostructure (**24a**), proposed earlier[16] for compound (**24**).

For a compound like (**24a**), the contributions of conformations *a* and *c* to the conformational equilibrium could be expected to be approximately equal. In conformation *a* the C-1 ethyl substituent is in the axial

position, which is energetically less favorable *per se* but allows the strong interaction with the indolic part of the molecule to be avoided. The bulky C-2 substituent would then be in an energetically unfavorable axial position. In conformation *c* the bulky C-2 substituent would be in an energetically favorable equatorial position, but there would be interaction between the equatorial C-1 ethyl substituent and the indolic part of the molecule (Scheme 20). As the measured shift values of compound (**24**) indicate that the molecule exists nearly totally in conformation *a*, the proposed[16] stereostructure (**24a**) cannot be accepted.



Scheme 20. Conformational equilibrium of compound (**24a**).

1β-Ethyl-2β-malonylindolo[2,3-*a*]quinolizidine (24b) (corrected stereostructure)

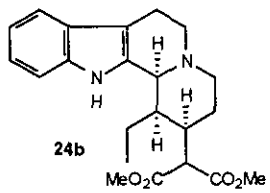
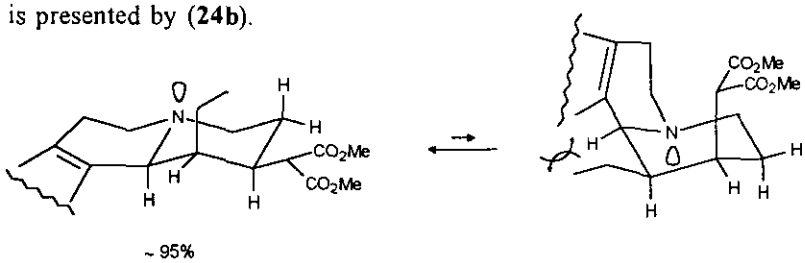


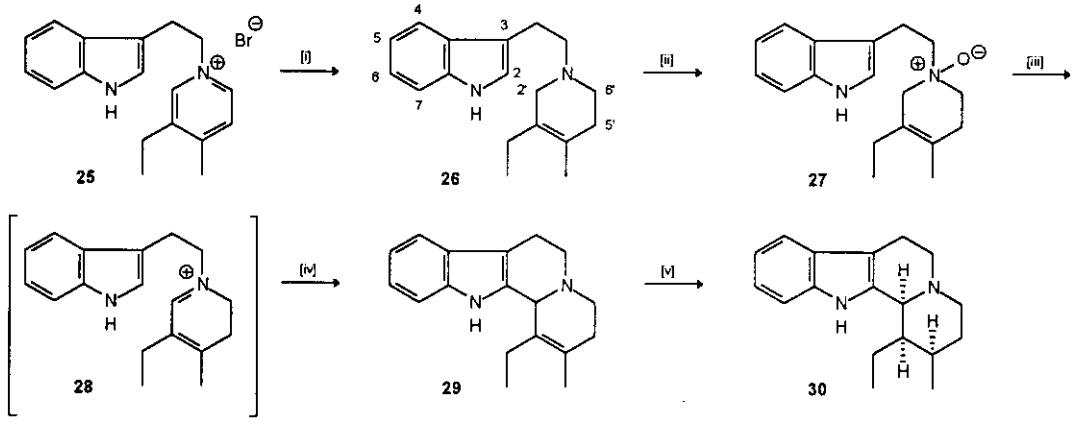
Figure 24. Corrected stereostructure (**24b**), now proposed for compound (**24**).

If compound (**24**) instead possessed the stereostructure (**24b**), the molecule would exist mostly (~95%) in conformation *a*. The C-1 ethyl substituent would be axial to avoid interaction with the indolic part of the molecule and the bulky C-2 substituent would be in the energetically more favorable equatorial position (Scheme 21). Accordingly, we now suggest that the correct stereostructure for compound (**24**) [compound (**30**) in Ref. 16] is presented by (**24b**).



Scheme 21. Conformational equilibrium of compound (**24b**).

To be quite sure that our conclusions concerning the stereostructure of compound (**24**) are correct we prepared model compound (**30**). Pyridinium salt (**25**)[23] was reduced with $NaBH_4$ to 1',2',5',6'-tetrahydropyridine (**26**)[24], which was oxidized by *m*-chloroperbenzoic acid (*m*-CPBA) to the corresponding *N*-oxide (**27**)[25]. Polonovski-Potier reaction (TFAA) followed by acid treatment led, *via* 5',6'-dihydropyridinium salt (**28**), to compound (**29**)[26]. Catalytic hydrogenation (H_2/PtO_2 -H_2O) of **29** afforded compound (**30**)[27] (Scheme 22).



Scheme 22. Preparation of compound (**30**) from compound (**25**), *via* compounds (**26**, **27**, **28**, and **29**). i. $NaBH_4$; ii. *m*-CPBA; iii. TFAA; iv. 1N HCl; v. H_2/PtO_2 -H_2O.

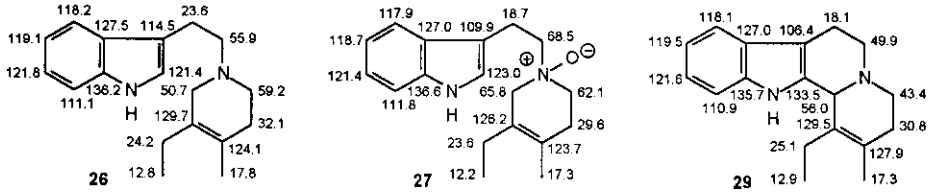


Figure 25. Measured ^{13}C NMR shift values of compounds (**26**, **27**, and **29**).

1β-Ethyl-2β-methylindolo[2,3-*a*]quinolizidine (30)

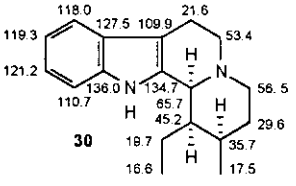
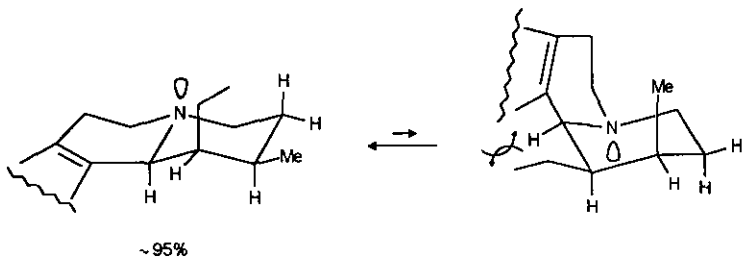


Figure 26. Measured ^{13}C NMR shift values of compound (**30**).

The shift value (C-7 δ 21.6 ppm) of compound (**30**) indicates, as could be expected, that it exists mostly (~95%) in conformation *a*. This permits the C-1 ethyl substituent to avoid interaction with the indolic part of the molecule and the C-2 substituent to be in equatorial position (Scheme 23).



Scheme 23. Conformational equilibrium of compound (**30**).

The shift values found for compound (**30**) are in excellent agreement with our conclusions that compound (**24**) possesses stereostructure (**24b**), and not (**24a**) as earlier[16] proposed (*vide supra*).

For comparison we also examined compounds (**31** - **34**).

2α-Malonyl-3β-ethylindolo[2,3-*a*]quinolizidine (31)

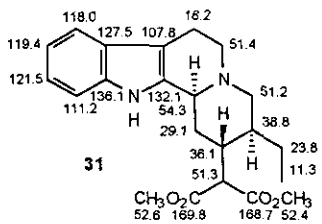
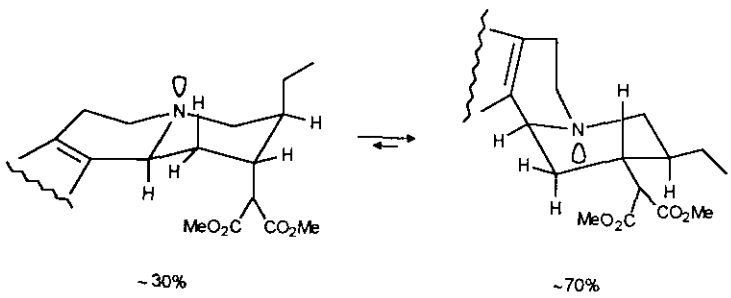


Figure 27. Measured ^{13}C NMR shift values of compound (**31**).[28]

Comparison of the measured[28] shift value δ 18.2 ppm (C-7) of compound (**31**) with the values δ 22.0 ppm and δ 16.6 ppm indicates that the contribution of conformers *a* and *c* to the conformational equilibrium is about 30% and 70%, respectively. In conformation *a* both substituents are in energetically unfavorable axial positions, whereas in conformation *c* they are in energetically more favorable equatorial positions (Scheme 24).



Scheme 24. Conformational equilibrium of compound (**31**).

2β-Methyl-3β-ethylindolo[2,3-*a*]quinolizidine (32)

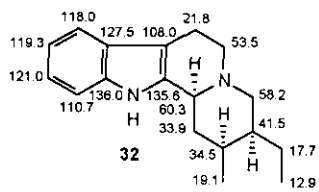
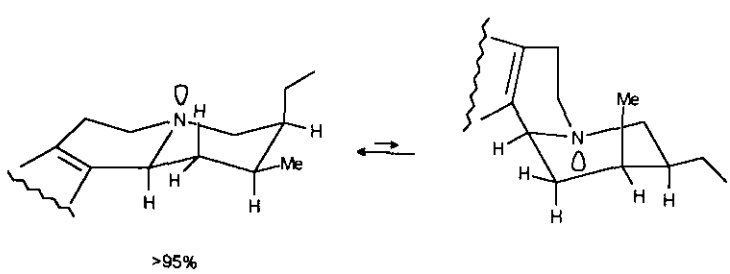


Figure 28. Measured ^{13}C NMR shift values of compound (**32**).[23]

Compound (**32**)[23] exists mostly (>95%) in conformation *a* (C-7 δ 21.8 ppm) although the C-20 ethyl substituent in this conformation occupies an axial position. In conformation *a* the C-2 methyl substituent is equatorial, which more or less compensates the unfavorable effect of the C-3 ethyl group in the axial position (Scheme 25).



Scheme 25. Conformational equilibrium of compound (**32**).

2β-Methyl-3α-ethylindolo[2,3-*a*]quinolizidine (33)

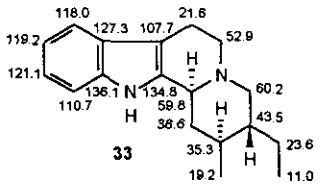
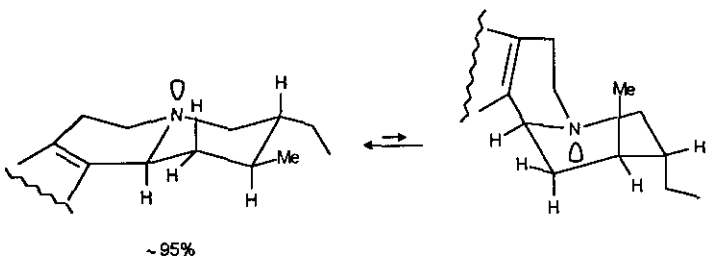


Figure 29. Measured ^{13}C NMR shift values of compound (**33**).[23]

Compound (**33**)[23] *exists* mostly (~95%) in conformation *a* (C-7 δ 21.6 ppm), where both substituents occupy the energetically more favorable equatorial position (Scheme 26).



Scheme 26. *Conformational equilibrium of compound* (**33**).

2α-Methyl-3α-ethylindolo[2,3-*a*]quinolizidine (34)

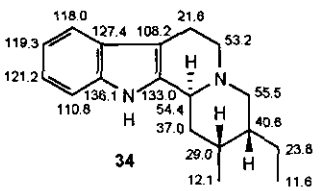
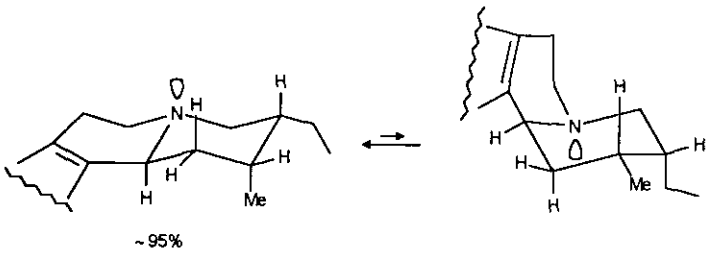


Figure 30. Measured ^{13}C NMR shift values of compound (**34**).[23]

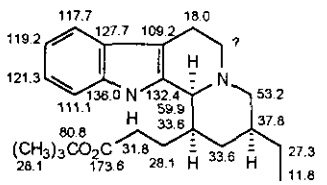
Compound (**34**)[23] exists mostly (~95%) in conformation *a* (C-7 δ 21.6 ppm) although the C-2 substituent in this conformation occupies an axial position. In conformation *a* the C-3 ethyl substituent is equatorial, which more or less compensates the unfavorable effect of the C-2 methyl group in axial position (Scheme 27).



Scheme 27. Conformational equilibrium of compound (**34**).

In connection with synthetic work on indole alkaloids of tacamine type, 1(2'-alkoxycarbonyl)ethyl-3-ethylindolo[2,3-*a*]quinolizidines (**35-38**) were prepared.[29,30] As these four compounds represent an interesting test case for a conformational examination of the present type, they are examined here in detail.

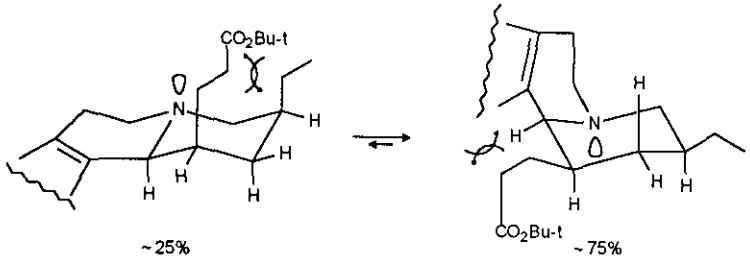
1β-(2'-*tert*-Butoxycarbonyl)ethyl-3β-ethylindolo[2,3-*a*]quinolizidine (35)



35

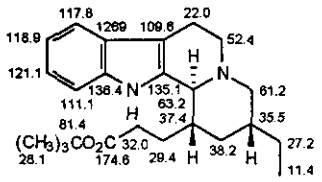
Figure 31. Measured ^{13}C NMR shift values of compound (**35**) (C-6 signal was not given).[29]

Comparison of the measured[29] shift value δ 18.0 ppm (C-7) of compound (**35**) with the values δ 22.0 ppm and δ 16.6 ppm indicates that the contributions of conformers *a* and *c* to the conformational equilibrium are about 25% and 75%, respectively. In conformation *a* both substituents are in the axial position, which is energetically less favorable *per se*. Moreover, there is a strong reciprocal interaction (diaxial 1,3-interaction) between the substituents. In conformation *c*, on the other hand, there is a strong interaction between the C-1 substituent and the indolic part of the molecule (Scheme 28). Evidently, in its conformational preference the molecule is behaving in accordance with Socrates' precept to choose the lesser evil.[31]



Scheme 28. Conformational equilibrium of compound (**35**).

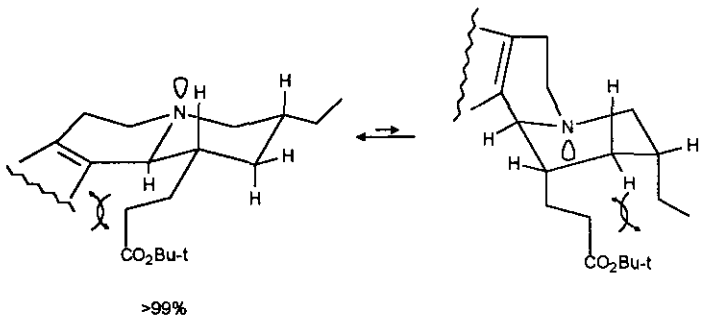
1α-(2'-*tert*-Butoxycarbonyl)ethyl-3α-ethylindolo[2,3-*a*]quinolizidine (36)



36

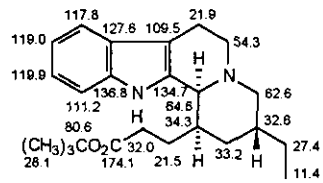
Figure 32. Measured ^{13}C NMR shift values of compound (**36**).[29]

Compound (**36**)[29] exists almost totally (>99%) in conformation *a* (C-7 δ 22.0 ppm). Both C-1 and C-3 substituents are in the energetically more favorable equatorial positions, although there is an unfavorable interaction between the C-1 substituent and the indolic part of the molecule. In conformation *c* both substituents are in the energetically less favorable axial positions and the substituents are in strong interaction with each other (diaxial 1,3-interaction)(Scheme 29).



Scheme 29. Conformational equilibrium of compound (**36**).

1β-(2'-*tert*-Butoxycarbonyl)ethyl-3α-ethylindolo[2,3-*a*]quinolizidine (37)

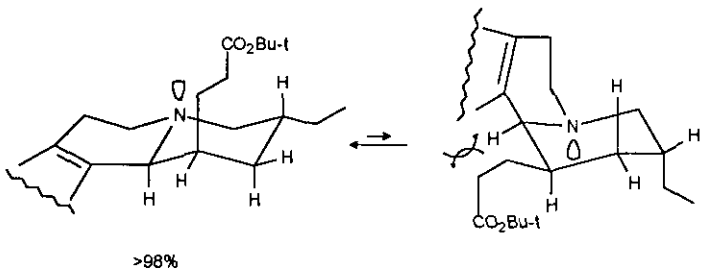


37

Figure 33. Measured ^{13}C NMR shift values of compound (**37**).[29]

Compound (**37**)[29] exists almost totally (>98%) in conformation *a* (C-7 δ 21.9 ppm). In conformation *a* the

C-1 substituent is in axial position and avoids interaction with the indolic part of the molecule. Moreover, the C-3 ethyl substituent is in the energetically more favorable equatorial position (Scheme 30).



Scheme 30. Conformational equilibrium of compound (**37**).

1α-(2'-Methoxycarbonyl)ethyl-3β-ethylindolo[2,3-*a*]quinolizidine (38)

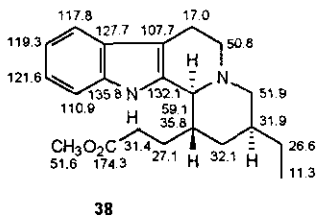
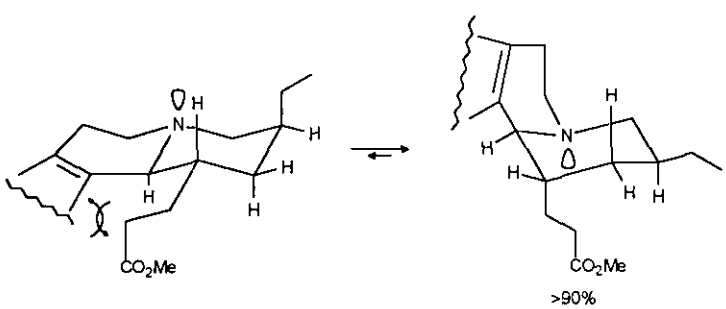


Figure 34. Measured ^{13}C NMR shift values of compound (**38**).[30]

Compound (**38**)[30] exists mostly (>90%) in conformation *c* (C-7 δ 17.0 ppm). The C-1 substituent is in axial position and thus avoids the strong interaction with the indolic part of the molecule which is present in conformation *a*. Moreover, the C-3 ethyl substituent is in the energetically more favorable equatorial position, whereas in conformation *a* it is in the less favorable axial position (Scheme 31).



Scheme 31. Conformational equilibrium of compound (**38**).

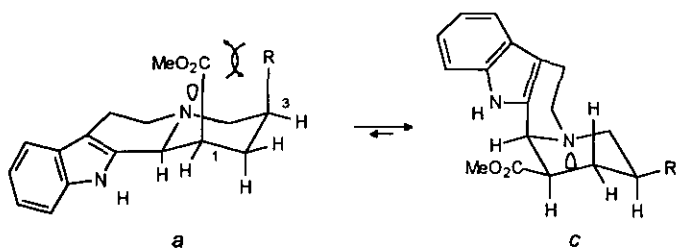
CONCLUSIONS

The conformational behavior of most substituted indolo[2,3-*a*]quinolizidines can be predicted with good accuracy by keeping in mind the following general rules:

1° Stability of conformer *a per se* is higher than that of conformer *c*.

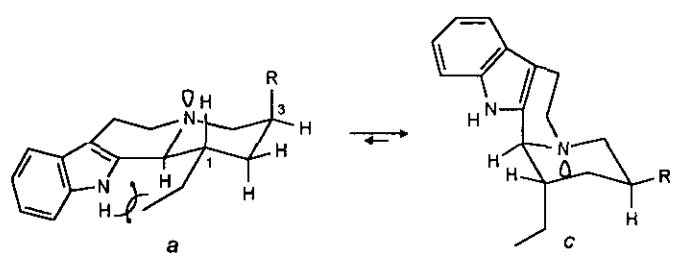
2° Substituents at C-1, C-2, and C-3 generally prefer an equatorial position, although their reciprocal interactions may complicate the situation (*vide infra*).

3° Interactions between axial substituents at C-1 and C-3 (diaxial 1,3-interaction) may strongly influence the conformational equilibrium (Scheme 32).



Scheme 32. Interaction between axial substituents at C-1 and C-3.

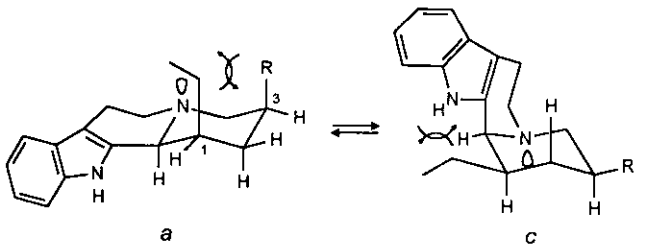
4° Interactions between equatorial alkyl (and similar) substituents at C-1 and the indolic part of the molecule may influence the conformational equilibrium (Scheme 33). The situation is completely different for methoxycarbonyl (and similar) groups (*vide supra*).



Scheme 33. Interaction between equatorial ethyl substituent at C-1 and the indolic part of the molecule.

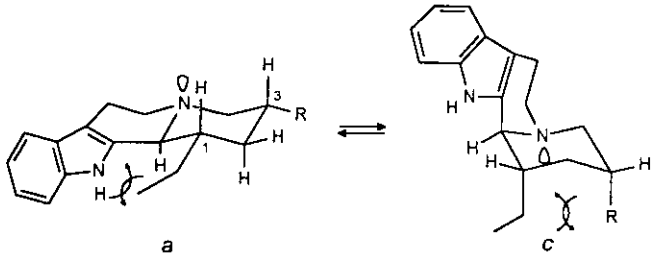
5° For C-1 ethyl (alkyl and similar) substituents (Schemes 34 and 35) the two above phenomena (3° and 4°) may also be conflicting, in which case it will be more difficult to predict the dominant

conformation. Evidently, in these cases the molecules will behave in accordance with the Socratic precept to choose the lesser evil.[31]



a *c*

Scheme 34. Opposite effects due to diaxial substituents at C-1 and C-3 (conformation *a*) and equatorial ethyl substituent at C-1 (conformation *c*).



a *c*

Scheme 35. Opposite effects due to equatorial ethyl substituent at C-1 (conformation *a*) and diaxial substituents at C-1 and C-3 (conformation *c*).

In addition, hydrogen bond formation of appropriate substituents with N_a or N_b (without importance in the present cases) has occasionally to be taken into consideration (*vide supra*).

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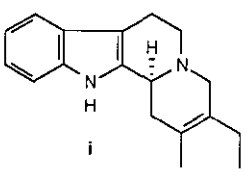
24. Compound (**26**). Yield: 100%. Amorphous. ^{1}H-NMR: 0.99 (3H, t, J=7.6 Hz, -CH_2CH_3), 1.65 (3H, br s, -CH_3), 2.02 (2H, q, J=7.6 Hz, -CH_2CH_3), 6.98 (1H, d, J=2 Hz, H-2), 7.11 (1H, td, J_1=8 Hz, J_2=1.2 Hz, H-5), 7.18 (1H, td, J_1=8 Hz, J_2=1.2 Hz, H-6), 7.32 (1H, dd, J_1=8 Hz, J_2=1.2 Hz, H-7), 7.62 (1H, d, J=8 Hz, H-4), 8.15 (1H, br s, NH). MS: 268 (M^+), 138 (100 %), 130. HRMS: Calcd for $C_{18}H_{24}N_2$ 268.1939. Found 268.1943.

25. Compound (**27**). Yield: 48%. Amorphous. ^{1}H-NMR: 0.92 (3H, t, J=7.6 Hz, -CH_2CH_3), 1.67 (3H, s, -CH_3), 2.21 (2H, q, J=7.6 Hz, -CH_2CH_3), 7.00 (1H, d, J=1.2 Hz, H-2), 7.02 (1H, t, J=8 Hz, H-5), 7.10 (1H, t, J=8 Hz, H-6), 7.42 (1H, d, J=8 Hz, H-7), 7.50 (1H, d, J=8 Hz, H-4), 10.88 (1H, br s, NH). MS: 284 (M^+), 268, 143 (100%). Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.12; H, 8.62; N, 9.96.

26. Compound (**29**): Yield: 22%. Amorphous. ^{1}H-NMR: 1.09 (3H, t, J=7.4 Hz, -CH_2CH_3), 1.70 (3H, s, CH_3), 4.65 (1H, br s, H-12b), 7.06-7.15 (2H, m, H-9, H-10), 7.33 (1H, d, J=7 Hz, H-11), 7.46 (1H, d, J=7 Hz, H-8), 8.12 (1H, br s, NH). MS: 266 (M^+, 100%), 237, 138. HRMS: Calcd for $C_{18}H_{22}N_2$ 266.1783. Found: 266.1763.

Small amounts (10%) of the "outside" isomer (**i**) of compound (**29**) were isolated as well. For the analytical data, see Ref. 23.



i

27. Compound (**30**): Yield: 43%. Amorphous. ^{1}H-NMR: 0.80 (3H, t, J=7.5 Hz, -CH_2CH_3), 1.05 (3H, d, J=6.5 Hz, >$CHCH_3$), 3.30 (1H, d, J=2 Hz, H-12b), 7.06-7.19 (2H, m, H-9, H-10), 7.33 (1H, dd, J_1=7.5 Hz, J_2=2 Hz, H-11), 7.49 (1H, dd, J_1=7.5 Hz, J_2=2 Hz, H-8), 7.68 (1H, br s, NH). MS: 268 (M+, 100%), 267, 253, 239, 197, 184, 170, 169. HRMS: Calcd for $C_{18}H_{24}N_2$ 268.1939. Found 268.1924.

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Received, 22nd February, 1999