Stereochemical Assignments

Due to the presence a sp^3 hybridized N atom in saturated 19-nor-10-azasteroids, one of the problems encountered in assigning their relative stereochemistry is the determination of the type (i.e. cis or trans) of fusion between rings A and B. In benzo[c]quinolizin-3-ones **1-18**, lacking the conjugation with the 3-oxo group through a double bond in the A ring, the bridgehead N atom should share its lone pair with the aromatic ring, thus changing its hybridization toward sp^2. As a consequence, in these compounds only the relative stereochemistry of the substituents on the A and B ring to the 4a-H hydrogen atom must be determined. Semi-empirical AM1 studies on model compound **1** confirmed our initial assumption, since in the global minimum conformer the nitrogen atom has an intermediate hybridization between sp^2 and sp^3 with bond angle values of 111.4, 117.0, and 117.7°. In this conformer, the A ring is in a chair-like conformation (Figure 1). The ^{1}H NMR spectrum of compound **1**, after the unambiguous attribution of all signals by HETCOR, and COSY experiments, is consistent with the results of the calculations. In particular, concerning the A ring, two sets of signals at 4.22 and 3.17 ppm are attributable to the protons on C-1 while the multiplet at 3.48 ppm is assignable to the bridgehead 4a-H. The signal at 4.22 ppm is a ddd, with J = 13.6, 6.2, and 3.3 Hz. The occurrence of only one large (13.6 Hz) geminal coupling constant with the other proton on C-1, and two small vicinal ones (6.2 and 3.3 Hz) with the protons on C-2, can be accounted for by assuming an equatorial position for the proton resonating at 4.22 ppm (1-H_{eq}). The other proton on C-1 (1-H_{ax}) must be axially orientated since, besides the large geminal coupling (13.6 Hz), its signal is further split by another large constant (11.4 Hz) attributable to a diaxial coupling with a proton on C-2. The last J is small (3.7 Hz) corresponding to an axial-equatorial type coupling. The values of J measured for the protons on the A ring are consistent with the predicted chair-like conformation for the A ring and the calculated coupling constant for the global minimum conformer resulted very close to those experimentally found. In a possible boat-like conformation, apart from the geminal coupling, both protons on C-1 would presents small coupling constants with the protons on C-2 due to the axial-equatorial or equatorial-equatorial relationship. The NOESY cross-peak between 4a-H and 1-H_{ax} further confirm the axial orientation of both protons.

The equatorial or axial orientation of the substituents (methyl groups) on the A and B rings in saturated compounds **4-18** could be assigned by the coupling constant values in the ^{1}H NMR spectrum. However, this is not always possible due to the complexity of the spectra of the saturated compounds.

Instead, the stereochemistry may be easily assigned in the corresponding $\Delta^{1,2}$ unsaturated compounds (Figure 1), wherein the relative orientation of the 4- and 5-methyl groups to the proton on 4a does not change after the oxidation. The oxidation to the corresponding $\Delta^{1,2}$ compounds causes in fact deshielding of the proton on C-4a therefore making the determination of the coupling constants of this proton with the other vicinal one much easier. For the diastereomeric pairs **4-5**, **6-7**, and **8-9**, the relative stereochemistry generated by the introduction of a methyl group on C-4 is not attributable through the analysis of the coupling constants between the proton on C-4 and C-4a but on the basis of some considerations concerning the chemical shifts of the protons. In 4α-Me isomers **4**, **6**, and **8** the equatorial methyl group causes a noticeably shielding of axial 4a-H that resonates at about 3.1 ppm (this proton resonates at ~ 3.5 ppm in **1-3**). The same effect of shielding of an equatorial methyl group on 4a-H is observed in all 5α-Me derivatives (see later). Moreover, in compounds **5**, **7** and **9**, the axial 5β methyl group is on the same side of the residual N lone pair and resonates at lower fields (~ 1.2 against ~ 1.0 ppm) than in their equatorially substituted isomers. This attribution was confirmed after oxidation of the saturated compounds **4-5** and **6-7** to the corresponding $\Delta^{1,2}$ pairs **22-23** and **24-25**: the 4a-H proton resonates at ~ 3.63 ppm in **22** and **24** as a ddd with two large (~ 12.5 Hz) and one small (~ 4.5 Hz) coupling constants, whereas in **23** and **25** 4a-H is a ddd at ~ 4 ppm with two coupling constant values lower than 5 Hz and one large (about 12 Hz). Being 4a-H axially orientated, these data can be accounted for only by assuming that the methyl group in **22** and **24** is equatorial (and axial in **23** and **25**). Moreover, in compounds **23** the proton on C-4 presents a small allylic coupling (1.1 Hz) with the proton on C-2, which is possible only if 4-H is in the plane of the C-1—C-2 double bond, i.e. equatorial. In the case of compound **26**, deriving from the oxidation of **9**, the β axial orientation for the 4-methyl group can be assigned in a similar fashion, since 4a-H is a multiplet at 4.03 ppm with two J values lower than 5 Hz and one ~ 13 Hz. Moreover, 2-H is a doublet of doublets because of the allylic coupling with the equatorial 4-H proton. Interestingly, the equatorial methyl group in **22** and **24** is more deshielded by 0.1-0.2 ppm compared to the methyl in **23** and **25**, perhaps due to the fact that it lies on the plane of the molecule.

The assignment of the exact stereochemistry in 1-methyl substituted compounds is of secondary importance, since **13** and **14** are obtained as an inseparable mixture then oxidized to final compounds **30** and **44** which do not present any relative stereochemistry between the methyl group and 4a-H.

In 5-methyl substituted benzo[c]quinolizin-3-one **27**, the coupling constant value (10.9 Hz) of 4a-H (at 3.61 ppm) with 6-H is consistent with the equatorial α stereochemistry of the methyl group. The

same stereochemistry can be thus attributed to corresponding saturated compound **10**, in the spectrum of which it is also appreciable the shielding effect of the equatorial 5α-Me on 4a-H. In the corresponding 5β isomer (from the crude reaction mixture) 4a-H resonates at 4.07 ppm due to the deshielding effect of the axial 5β methyl group and presents a low coupling constant (4.0 Hz) with 6-H consistent with the axial orientation of the methyl.

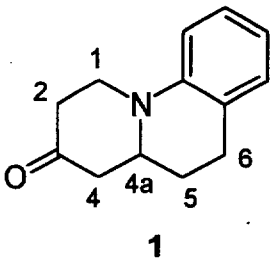
The stereochemistry of 6-methyl derivatives has been assigned on $\Delta^{1,2}$ unsaturated compounds **28-29** by the usual analysis of the coupling constants of 6-H (resonating at 3.0 ppm) with the two vicinal protons: two small *J* values (< 4-5 Hz) are consistent with the equatorial position of this proton, i.e. the α axial orientation of the methyl group. The same 6α-Me stereochemistry must therefore be assigned to the corresponding saturated compounds **11** and **12**

The relative stereochemistry to the 4,5-dimethyl and 4,6-dimethyl derivatives has been once again assigned only on $\Delta^{1,2}$ unsaturated compounds on the basis of the coupling constant values. In 4,5-dimethyl derivative **31** the proton on C-4a resonates at 3.15 ppm as a doublet of doublets and has two large *J* values (8.4 and 8.5 Hz) with the axial vicinal protons on C-4 and C-6, consistent with the α equatorial position of both the methyl groups on C-4 and C-5. In its epimer **32** proton 4a-H resonates at 3.64 ppm as a doublet of doublets with one large diaxial coupling constant with the proton on C-6 (11.4 Hz) and one small (3.0 Hz) with the equatorial proton on C-4. Thus, in **32**, the methyl on C-4 is β axially orientated. Consistent with this attribution, the α equatorial 4-methyl group in **31** is more deshielded and resonates at 1.29 ppm, while the β axial one in **32** at 1.15 ppm, being out of the plane of the molecule. On the other hand, since its stereochemistry does not change, the methyl group on C-5 resonates at 1.00 ppm in both compunds. In the case of saturated compound **15** the assignment of relative 4α,5α stereochemistry was possible also on the saturated compound: the combined shielding effect of the two equatorial methyl groups cause a strong shielding of 4a-H to ~ 2.50 ppm. Moreover, both the methyl groups resonate at ~ 1.0 ppm, being on the opposite site of the N lone pair, whereas in compound **16** the 4β methyl group resonates at 1.10 ppm.

In 4,6-dimethyl derivatives **33** and **34**, the α axial position of the methyl group at position 6 has been assigned based on the coupling constant of 6-H with the vicinal protons on C-5. The occurrence of no large coupling constants with any of the protons on C-5 (*J* values of 6.2-6.9 Hz with the methyl group, all the other lower than 4 Hz) appears consistent with the above attribution and, again, with the preferred anti approach of the diene to the methyl group at position 5 or 6. Moreover 6-H resonates at 3.0 ppm and the geminal methyl group at 1.20-1.30 ppm, as in compounds **28** and **29** which present the

same stereochemistry concerning the B ring. Finally, the α equatorial orientation of the 4-methyl group in both the products is assigned on the basis of the large *J* value between 4-H with 4a-H (16.8 Hz) which are in a trans diaxial relationship.

Figure 1



1