Stereochemical Assignments in Steroids by ^{13}C Nuclear Magnetic Resonance Spectroscopy: Configuration of the A/B Ring Junction

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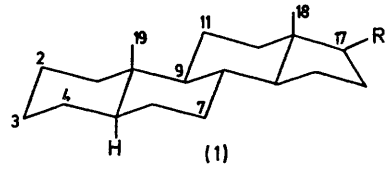
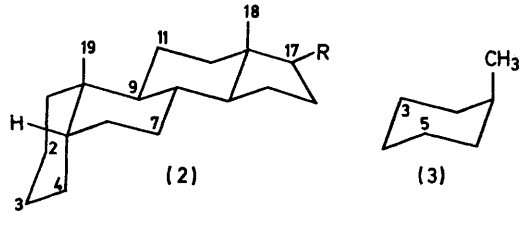
Summary The shielding of the steroidal C-19 methyl carbon directly signals the stereochemistry of the A/B ring junction; its absorption position differs by 11—12 p.p.m. between 5α- and 5β-steroids.

THE marked sensitivity of ^{13}C n.m.r. shieldings to molecular geometry has been well established from studies of several simple alicyclic and bicyclic systems[1] and the utility of this stereochemical dependence for signal assignments in the spectra of moderately complex compounds clearly demonstrated.[2] The analysis of the ^{13}C spectra of a series of steroids by Roberts and his co-workers[3] is a particularly elegant example of this application and their body of data provides a good basis for the analysis of the ^{13}C spectra of related materials. Their series, however, was restricted to Δ^4- and 5α-steroids and included no compounds having the *cis*-A/B ring fusion, the 5β-steroids. Since pronounced shielding differences may be expected for



(1)



(2)

(3)

certain carbons in the A and B rings and for C-19 in the 5α- and 5β-series, (1) and (2), respectively, ^{13}C spectroscopy offers a new method for stereochemical assignment in such systems. Although the angular methyl proton shieldings permit this assignment in many systems,[4] there are cases in which the C-19 protons absorb in essentially the same position for both 5α- and 5β-steroids. In contrast, the ^{13}C shielding differences are marked in all cases so far examined.

TABLE

C-19 *Methyl carbon shielding differences in 5α- and 5β-steroids*

Substitution			C-19
C-3	C-11	C-17	$\Delta\delta_{5\beta-5\alpha}$
—	—	—	12·0
—	—	C_2H_5	12·0
—	—	C_8H_{17}	12·0
—	β-OH	C_2H_5	12·3
—	α-OH	C_2H_5	11·8
—	=O	C_2H_5	12·0
β-OH	—	C_8H_{17}	11·5
β-OH	—	$CH(OH)CH_3$	11·8
β-OH	—	=O	11·5
β-OH	—	β-OH	11·8
α-OH	—	β-OH	12·1
α-OH	—	=O	12· 1
=O	—	$COCH_3$	11·2
=O	=O	$COCH_3$	11·3
=O	—	=O	11·1
=O	—	β-OH	11·1
=O	—	C_8H_{17}	11·2

We present ^{13}C data illustrating the direct and unambiguous assignment for the A/B ring fusion from the angular methyl carbon shieldings and indicate the supporting evidence provided by the relative shieldings for some of the skeletal carbon nuclei.

In general, carbon nuclei in gauche vicinal orientations relative to another carbon or heteroatom absorb at significantly higher field than their counterparts in anti vicinal arrangements. For example, axial methylcyclohexane (3) exhibits methyl carbon absorption *ca.* 6 p.p.m. higher field than that of the equatorial conformer.[5] In the axial form, the methyl carbon is gauche with respect to carbons-3 and -5 while it is anti to these nuclei in the equatorial conformer. Several examples involving gauche vicinal interactions between carbon and oxygen have also been reported.[1] Thus, it follows that the C-19 methyl carbon shielding should clearly reflect the stereochemistry of the A/B ring fusion in 5α, and 5β-steroids since its gauche interactions

with carbons-2 and -4 in the former are absent in the 5β-series. The relative rigidity of the steroid skeleton is such that the C-18 shielding may be expected to be essentially unaffected by a change in the A/B ring fusion. Thus, a comparison of the C-18 and C-19 signals for isomeric pairs in the 5α- and 5β-series is straightforward with the C-18 signal common to both. Methyl carbons are easily distinguished from the others in these spectra by off-resonance decoupling and the methyl signals for the side-chain carbons are readily assigned by virtue of the insensitivity of their shieldings to structural changes in the A and B rings. The shielding differences observed for the C-19 nucleus in a variety of 5α- and 5β-steroids are listed in the Table.

For this assortment of substituents it is apparent that the stereochemistry of the A/B ring junction markedly affects the C-19 shielding. In all cases, C-19 is 11—12 p.p.m. *less* shielded in the 5β- steroids. This difference may be compared with the range found for the C-19 protons in the same systems, namely 0·008—0·15 p.p.m.[4] In fact, the differences observed for the C-19 shieldings are surprisingly large on the basis of the data for several substituted cyclohexanes[1,5] but the methyl shieldings in *cis*- and *trans*-9-methyldecalin differ by 12·4 p.p.m.[6] It is important to note that the C-19 shieldings are markedly lower in the 5β-series relative to those in Δ^4-steroids. A comparison of the data for several pairs in the 5α- and Δ^4-systems reveals that the double bond reduces the C-19 shielding by 6—7 p.p.m.; at least part of this shift is presumably due to the alteration in orientation between C-19 and C-4.

In these spectra the methine signals are as readily identified by off-resonance decoupling as those arising from methyl carbons and, since there are relatively few, their assignment to specific centres is straightforward on the basis of the model data now available. For 5α- and 5β-isomers a marked shielding difference is expected for C-9 since there are two gauche interactions (with C-2 and C-4) in 5β-systems which do not occur in the 5α-series. In complete accord with this the C-9 signal of the 5β-steroids is significantly upfield from its position in the spectra of the 5α-isomers. For the examples listed in the Table, the C-9 shielding differences lie in the range 11·8—14·6 p.p.m. Thus there are two easily distinguished signals in each of these spectra which provide a straightforward assignment of the stereochemistry of the A/B ring junction for a host of steroids. We emphasize that the relative shifts of the C-9 and C-19 signals are sufficiently large that one can determine the A/B ring geometry from the spectrum of an individual isomer if the effects of its substituents have been characterized as is the case for oxygen-containing groups at the 3-, 6-, 11-, 17-, and 20-positions. In the 3-oxo-steroids, one of the common structures for which the angular methyl proton shieldings are essentially identical for the 5α- and 5β-systems, the geometry of the A/B ring fusion is clearly indicated by the ^{13}C results (see Table). Although the shieldings of some additional centres in these compounds provide further supporting evidence, their assignment requires a complete spectral analysis which may not be unequivocal without an array of closely related compounds. The full analysis of the ^{13}C spectra of this series of steroids will be discussed elsewhere.

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