Substituted 4a-Methyloctahydrophenanthrenes: Conformation and Proton Magnetic Resonance Characteristics

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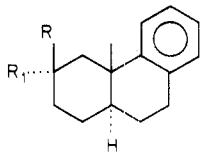
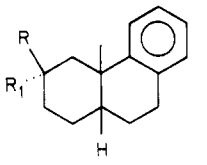
Received October 17, 1978

Analysis of the ^1H NMR resonance position of the 4a-methyl group of substituted 4a-methyloctahydrophenanthrenes allows an assignment of conformation of the overall ring system. With a series of reference positions established, it is possible to assign tentative stereochemistry to substituents in newly prepared or isolated substances.

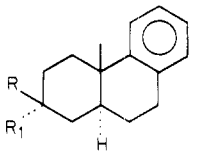
The availability of C-2- and C-3-substituted 4a-methyloctahydrophenanthrenes[1] as a result of synthetic



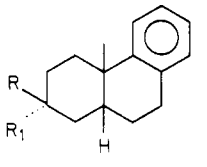
1a, R = R_1 = H
b, R = H; R_1 = OH
c, R = OH; R_1 = H
d, R = H; R_1 = OCOPh
e, R = OCOPh; R_1 = H
f, R = OTs; R_1 = H
g, R = H; R_1 = N_3
h, R = H; R_1 = NH_2
j, R = H; R_1 = $N(CH_3)_2$
k, R = $N(CH_3)_2$; R_1 = H



2a, R = R_1 = H
b, R = H; R_1 = OH
c, R = OH; R_1 = H
d, R = H; R_1 = OCOPh
e, R = OCOPh; R_1 = H
f, R = H; R_1 = OMs
g, R = H; R_1 = OTs
h, R = OTs; R_1 = H
j, R = H; R_1 = OAc
k, R = H; R_1 = N_3
l, R = N_3; R_1 = H
m, R = H; R_1 = NH_2
n, R = NH_2; R_1 = H
p, R = H; R_1 = $N(CH_3)_2$
q, R = $N(CH_3)_2$; R_1 = H



3a, R = R_1 = oxo
b, R = OH; R_1 = H
c, R = OTs; R_1 = H
d, R = H; R_1 = $N(CH_3)_2$
e, R = $N(CH_3)_2$; R_1 = H

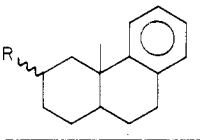


4a, R = R_1 = oxo
b, R = H; R_1 = OH
c, R = H; R_1 = OTs
d, R = $N(CH_3)_2$; R_1 = H
e, R = H; R_1 = $N(CH_3)_2$

studies in our laboratories prompted us to examine their spectral and conformational properties.[2]

The ^1H NMR spectra of 4a-methyloctahydrophenanthrenes are very useful for determining product ratios and stereochemistry. Wenkert and co-workers,[3] from extensive studies on natural products containing the 4a-methyloctahydrophenanthrene ring structure, have demonstrated that the C-4a-methyl group's chemical shift is extremely sensitive to changes in conformation and configuration. Wenkert and co-workers attempted to correlate the chemical shift of the C-4a-methyl group with the angle subtended by the plane of the aromatic ring and defined by the bonds between C-4a-, C-4b-, and the 4a-methyl group (Figure 1). In cases where this dihedral angle (hereafter referred to as angle *A*) approaches 90°,

Table I. 10aα, C-3-Substituted Compounds



compd no.	R	δ C-3-methine H ($W_{1/2}$ in Hz)	δ 4a-CH_3
1a	H		1.07
1b	α-OH	3.97 (18.0)	1.08
1c	β-OH	4.22 (8.0)	1.28
1d	α-BzO[a]	5.42 (18.0)	1.18
1e	β-BzO	5.40 (8.0)	1.29
1f	β-TsO[b]	4.85 (8.0)	1.17
1g	α-N_3[c]	3.51 (21.0)	1.05
1h	α-NH_2		1.08
1j	α-$N(CH_3)_2$		1.05
1k	β-$N(CH_3)_2$		1.25

[a] BzO = benzoate. [b] TsO = tosylate. [c] N_3 = azide.

the C-4a-methyl group is as far above the aromatic ring as possible within the constraints of the tricyclic system. This places the methyl group in the strongest shielding zone of the aromatic ring as evidenced by its chemical shift of 1.07 ppm in the trans hydrocarbon **1a**. Wenkert has gathered substantial evidence that ring B is in the twist-boat conformation,[3] and we can reasonably assume ring A is in the chair conformation. Having assigned the conformations of the A and B rings, we can determine angle *A*. Thus, by inspection of Drieding molecular models angle *A*, measured from C-8a, for hydrocarbon **1a** was 98 ± 2°.

The ^1H NMR chemical shifts of the C-4a-methyl and the C-3-methine hydrogens for the trans compounds are listed in Table I. The widths at half-height ($W_{1/2}$) of the C-3-methine hydrogens are also reported.

It has been firmly established[4] from spectra of numerous compounds containing six-membered rings or six-membered rings fused to other structures that for conformations which do not depart appreciably from the chair form, the *J*(axial–axial) coupling constant is in the range of 8–13 Hz, the *J*(axial–equatorial) coupling constant is in the range of 2–6 Hz, and the *J*(equatorial–equatorial) coupling constant is invariably smaller than that of the *J*(axial–equatorial) coupling by 1 Hz. Even in cases where the signal cannot be resolved due to virtual coupling (as is often the case with steroids and terpenes), the width of

† Taken in part from the dissertations presented by C. L. Spencer (1970) and A. L. Campbell (1978) to the Graduate School of the University of Kansas in partial fulfillment of the requirements of the degree Doctor of Philosophy.

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(1) A. L. Campbell, H. N. Leader, C. L. Spencer, and J. D. McChesney, *J. Org. Chem.*, preceding paper in this issue.

(2) The term cis will be used to designate compounds of the series 10aβ-H and trans to designate 10aα-H compounds.

(3) E. Wenkert, A. Afonso, P. Beak, R. Carney, P. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).

(4) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, New York, 1969 p 286.

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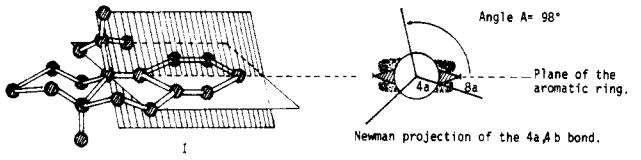


Figure 1. Definition of the shielding environment of the C-4a-methyl group of the 10α,4a-methyloctahydrophenanthrenes.

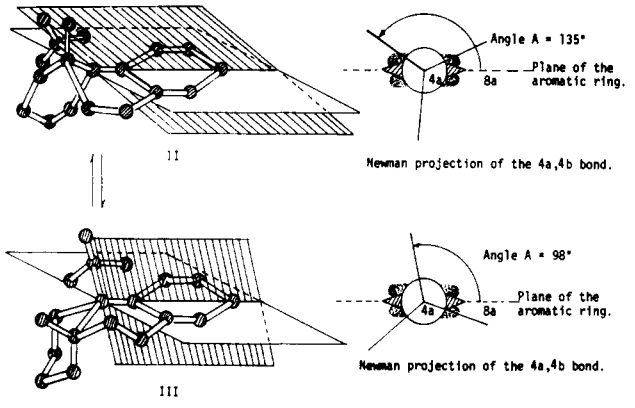


Figure 2. Definition of the shielding environment of the C-4a-methyl group of the 10β,4a-methyloctahydrophenanthrenes.

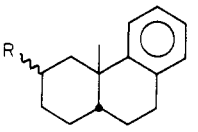
the multiplet at half-height ($W_{1/2}$) is highly characteristic, an axial proton generally having $W_{1/2}$ larger than 15 Hz.

Inspection of Table I reveals the C-4a-methyl chemical shifts for the variously C-3α-substituted compounds differ very little from hydrocarbon **1a** while the methyl signals for the C-3β isomers are substantially shifted downfield (0.21–0.10 ppm) when compared with **1a**. This downfield shift cannot be accounted for by differences in angle *A* for the α- and β-substituted compounds because this angle is held very nearly constant by the rigid trans ring juncture. It is evident from the value of $W_{1/2}$ (8.0 Hz) that ring A remains in the chair conformation even though the C-3β substituents introduce a severe 1,3 diaxial interaction with the C-4a-methyl group. Therefore, the deshielding affect of the C-3β (axial) substituent must be due to electronic interactions which are amplified by the substituent's close proximity to the angular methyl group. These electronic effects diminish rapidly with distance, thus the C-3α (equatorial) substituents do not affect the chemical shift of the 4a-methyl group.

The 4a-methyl and C-3-methine hydrogen ($W_{1/2}$) chemical shifts for the cis compounds are listed in Table II. In contrast to the rigid well-defined trans compounds, the conformation(s) of the cis isomers are much more difficult to describe due to the inherent flexibility of this ring system. The cis compounds can exist in two, or an equilibrium mixture of both, conformations, II and III.

In analogy with the trans ring system, it is reasonable to assume that ring A is in the chair conformation and ring B is in the twist-boat conformation. Then II and III represent the two extremes (limited by the constraints of the tricyclic ring system) resulting from interconversion of the two possible chair and twist-boat conformations. From molecular models, angle A for II and III was found to be 135 ± 2 and 98 ± 2°, respectively. Knowing that the larger the angle *A* value the more deshielded the 4a-methyl group becomes, one would predict the methyl signal of III to be very similar to the trans hydrocarbon **1a** (1.07 ppm, angle *A* 98°) and the methyl signal of II to be substantially further downfield (ca. 1.40 ppm). The actual 4a-methyl chemical shift for **2a** is 1.23 ppm.[3] This is consistent with approximately a 1:1 equilibrium mixture of conformations I and III which is reasonable because the energy barrier between the two conformations is undoubtedly small for the cis hydrocarbon.

Table II. 10aβ, C-3-Substituted Compounds



compd no.	R[a]	δ C-3-methine H ($W_{1/2}$ in Hz)	δ 4a-CH_3
2a	H		1.23
2b	α-OH	3.72 (24.0)	1.36
2c	β-OH	3.32 (18.0)	1.18
2d	α-BzO	5.28 (18.0)	1.41
2e	β-BzO	4.65 (18.0)	1.22
2f	α-MsO	4.80 (18.0)	1.38
2g	α-TsO	4.70 (20.0)	1.29
2h	β-TsO	4.03 (22.0)	1.10
2j	α-AcO	5.00 (21.0)	1.38
2k	α-N_3		1.35
2l	β-N_3		1.21
2m	α-NH_2		1.34
2n	β-NH_2		1.18
2p	α-$N(CH_3)_2$		1.36
2q	β-$N(CH_3)_2$		1.18

[a] BzO = benzoate; TsO = tosylate; MsO = mesylate; AcO = acetate.

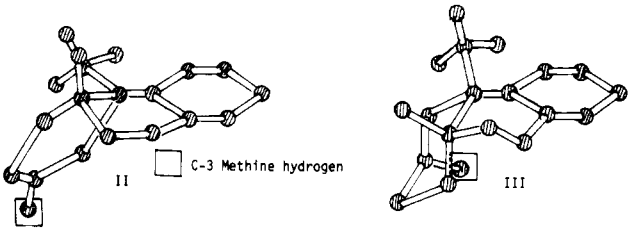
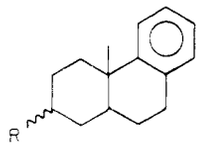


Figure 3. Proximity of the C-3-methine to the shielding environment of the aromatic ring C.

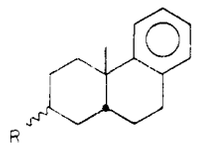
The effect of C-3 substituents on the position of the equilibrium between II and III can be ascertained from Table II. The most striking feature of all the cis compounds is their $W_{1/2}$ values of 18–24 Hz. This indicates that the C-3-methine hydrogen is predominately in the axial orientation with the larger C-3 substituent in the equatorial position. To fulfill these requirements, the equilibrium conformation of the C-3α-substituted compounds must approximate that of II, and the equilibrium conformation of the C-3β-substituted compounds must be shifted in the direction of III. As in the equatorially substituted C-3α trans compounds, electronic effects on the chemical shift of the 4a-methyl group of the cis compounds will be minimal. The chemical shift data in Table II are consistent with these conformational assignments. The C-3α compounds with methyl signals ranging from 1.41 to 1.29 ppm are substantially further downfield than the C-3β-substituted compounds (1.22–1.10 ppm). The observation that the methyl signals for the C-3β cis compounds are further downfield than the C-3α trans compounds (1.08–1.03 ppm) is indicative of the flexibility of the cis ring system. Further evidence for the C-3β compounds equilibrium conformation favoring III is obtained from the chemical shift of the C-3 methine hydrogen. It is evident from molecular models that this methine hydrogen is positioned directly below the shielding π-electron cloud of the aromatic ring in conformation III (Figure 3). Therefore, one would predict the position of C-3-methine hydrogens in the β-substituted compounds to be shifted upfield from those of the corresponding α-substituted materials. Examination of Table II reveals

Table III. 10aα, C-2-Substituted Compounds



compd no.	R	δ C-2-methine H ($W_{1/2}$ in Hz)	δ 4a-CH_3
1a	H		1.07
3a	oxo		1.32
3b	β-OH	3.45 (21)	1.10
3c	β-OTs	4.45 (21)	1.10
3d	α-$N(CH_3)_2$		1.08
3e	β-$N(CH_3)_2$		1.06

Table IV. 10aβ, C-2-Substituted Compounds



compd no.	R	δ C-2-methine H ($W_{1/2}$ in Hz)	δ 4a-CH_3
2a	H		1.23
4a	oxo		1.40
4b	α-OH	3.50 (22)	1.13
4c	α-OTs	4.50 (22)	1.16
4d	β-$N(CH_3)_2$		1.31
4e	α-$N(CH_3)_2$		1.15

this to be the case. Although lack of sufficient data precludes the definitive assignment of the conformations of these cis compounds, the preliminary data are consistent enough to warrant further investigation.

The ^1H NMR chemical shifts of the C-4a-methyl and the C-2-methine hydrogens for the trans C-2-substituted compounds and the cis C-2-substituted compounds are listed in Tables III and IV, respectively. The widths at half-height of the methine resonances are also recorded. Although there are fewer compounds represented in the C-2 substituted series, their ^1H NMR characteristics support the conclusions reached in the case of the C-3-substituted materials.

The methine resonances of alcohol **3b** and tosylate **3c** (δ 3.45 and 4.45, respectively, both with half-band widths of 21 Hz) confirm that the C-2 substituent is equatorial. The C-4a-methyl resonances of both **3b** and **3c**, both at δ 1.10, indicate that the conformation of the ring system is very like the unsubstituted trans hydrocarbon **1a**. The equatorial C-2 substituents are directed away from the C-4a-methyl and have essentially no effect upon its resonance position. That a C-2 functional group may affect the resonance position of the C-4a methyl is shown in the case of the keto compounds **3a**. Its C-4a-methyl resonance of δ 1.32 is substantially downfield and indicates that the methyl lies in the deshielding region of the ketone anisotropy. The C-2α-dimethylamino derivative **3d** is not significantly distorted since its 4a-methyl resonance position (δ 1.08) is very similar to the unsubstituted model **1a** and the equatorial isomer **3e** (δ 1.06). That these isomers are axial and equatorial, respectively, is supported by the chemical shifts of the (*N,N*-dimethylamino)methyl resonances at 2.16 and 2.25. It is commonly observed that equatorial substituents are deshielded relative to axial isomers.[5]

As in the case of the C-3-substituted series, we would expect the conformation(s) of the C-2-substituted cis isomers to be more difficult to define relative to the trans isomers due to the inherent flexibility of this ring system. This expectation is evidenced by an analysis of the chemical shifts of the C-4a-methyl in the C-2-substituted cis series. The direct reductive amination of ketone **4a** produces a mixture of *N,N*-dimethylamino derivatives with C-4a-methyl resonances of δ 1.15 and 1.31. The difficulty of separation by chromatography suggests that the polar dimethylamino group is similarly exposed in both, i.e., equatorial. Inspection of models indicates that the C-2α isomer, to be equatorial, would place the C-4a-methyl above the aromatic ring (δ 1.15) whereas the C-2β isomer, when in the equatorial position, places the C-4a-methyl more in the plane of the aromatic ring (δ 1.31). Alcohol **4b** and tosylate **4c** have C-2-methine resonances at δ 3.50 and 4.50 with half-band widths of 22 Hz which indicates the equatorial nature of the C-2 substituent. The resonance position of the C-4a-methyl at δ 1.13 and 1.16, respectively, indicates that these are C-2α with a conformation placing the C-4a-methyl in the more shielding position above the aromatic ring. Displacement of the tosylate produces the C-2β-(*N,N*-diethylamino)octahydrophenanthrene which then undergoes a conformational change to an equatorial position which places the C-4a-methyl group more nearly in the plane of the aromatic ring yielding a resonance position of δ 1.31.

In conclusion, it is clear that the ^1H NMR resonance position of the C-4a-methyl in substituted 4a-methyloctahydrophenanthrenes gives a sensitive indication of their conformation and/or stereochemistry. With a knowledge of the stereochemistry of the A/B ring juncture (cis or trans), one may assign from an analysis of the position of the methyl resonance both relative stereochemistry and conformation of C-2 or C-3 substituents. Work is in progress to determine if C-1-, C-4-, and C-10-substituted 4a-methyloctahydrophenanthrenes may similarly be assigned.

Experimental Section

Proton magnetic resonance spectra were obtained with a Varian Associates EM-360 spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal standard. In ^1H NMR descriptions, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and dd = doublet of doublets.

All compounds have been previously described.[2] Satisfactory elemental analyses, spectral properties, and physical constants were obtained.

Registry No. **1a**, 70561-39-6; **1b**, 70524-64-0; **1c**, 70524-65-1; **1d**, 70524-66-2; **1e**, 70524-67-3; **1f**, 70524-68-4; **1g**, 70524-69-5; **1h**, 70524-70-8; **1j**, 70524-71-9; **1k**, 70524-72-0; **2a**, 60795-73-5; **2b**, 70524-73-1; **2c**, 70524-74-2; **2d**, 70524-75-3; **2e**, 70524-76-4; **2f**, 70524-77-5; **2g**, 70524-78-6; **2h**, 70524-79-7; **2j**, 70524-80-0; **2k**, 70524-81-1; **2l**, 70524-82-2; **2m**, 70524-83-3; **2n**, 70524-84-4; **2p**, 70524-85-5; **2q**, 70524-86-6; **3a**, 1686-50-6; **3b**, 70524-87-7; **3c**, 70524-88-8; **3d**, 70524-89-9; **3e**, 70524-90-2; **4a**, 70524-91-3; **4b**, 70524-92-4; **4c**, 70524-93-5; **4d**, 70524-94-6; **4e**, 70524-95-7.

(5) Reference 4, p 238.