Spectroscopic Study of 3-Methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-α(β)-ols

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Received September 20, 1991

3-Methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-α(β)-ols have been synthesized and studied by ir, ^{1}H and ^{13}C nmr spectroscopy. In deuteriochloroform and perdeuteriobenzene solutions, these compounds adopt a flattened chair-chair conformation in which the cyclohexane ring is more flattened.

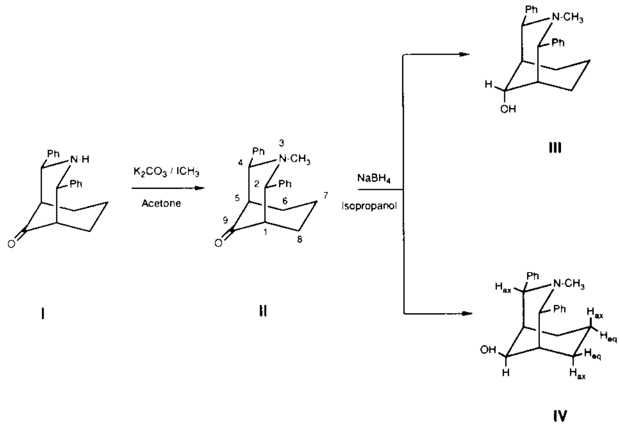
From the ^{1}H and ^{13}C nmr data, several stereoelectronic effects have been deduced. The complete and unambiguous assignment of all protons of the 3-azabicyclo[3.3.1]nonane system, not described up to date, has been carried out.

J. Heterocyclic Chem., **29**, 519 (1992).

Introduction.

Previous papers [1,2,3] reported the synthesis, ^{1}H nmr, ^{13}C nmr, ir studies and X-ray diffraction data for 3-phenethyl-3-azabicyclo[3.2.1]octan-8-α(and β)-ols, and 3-phenethyl-3-azabicyclo[3.3.1]nonan-9-α(and β)-ols and several esters derived from them [4]. In a research program devoted to the development of new 5-HT$_3$ receptor antagonists, we have synthesized 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-α(and β)-ols (Scheme 1). By comparing the ir and nmr parameters of the title compounds with those of the 3-methyl-3-azabicyclo[3.3.1]nonan-9-α(and β)-ols [3], several stereoelectronic effects have been deduced.

Scheme 1



Synthesis.

The synthesis of the title compounds is shown in Scheme 1. By treatment of the ketone **I** [5] with methyl iodide [6], compound **II** was obtained. From reduction of **II** with sodium borohydride [6] compounds **III** and **IV** were obtained.

EXPERIMENTAL

All melting points were taken in open capillary tubes in an Electrothermal IA6304 apparatus, and are uncorrected. The elemental analyses were made in a Perkin-Elmer Elemental Analyzer model 240E. The ir spectra were recorded on a Perkin-Elmer 883 spectrophotometer in the solid state (potassium bromide).

The ^{1}H nmr spectra of ~4% (w/v) deuteriochloroform or perdeuteriobenzene solutions of **III** and **IV** were recorded at 300 MHz using a Varian UNITY-300 spectrometer. Spectral parameters included sweep widths of 4000 Hz in 24 K memory and acquisition times of 3.0 s over 64 transients. Resolution enhancement using LB = −0.80, GF = 0.50 and GFS = 0.20 was followed by zero filing into 32 K memory prior to Fourier transformations. Conventional irradiation was used for the double resonance experiments in the same solvents.

The ^{13}C nmr spectra were obtained at 75.429 MHz on a Varian UNITY-300 spectrometer at a spectral width of 16501 Hz in 64 K memory, acqusition time of 1 s and relaxation delay of 1 s, using *ca.* 20% (w/v) deuteriochloroform solution. Two types of spectra were recorded: proton-noise decoupled spectra (to determine the chemical shifts) and off-resonance decoupled spectra (to help assign the signals).

All measurements were done at 298°K using TMS as internal reference.

Compounds I-IV.

The synthesis and purification of compounds **I-IV** have previously been described [5,6]. In this case, the separation of compounds **III** and **IV** was carried out by crystallization from hexane. The physical properties of compounds **I-IV** are in agreement with those reported [5,6].

Results and Discussion.

Based only on ^{13}C δ values of compounds **III** and **IV**, Jeyaraman *et al.* [7] reported a configuration for the pair of epimers **III** and **IV**, which was opposed to that suggested by another authors [6,8,9] on the basis of less conclusive methods (order of elution on column chromatography [6], relative rates of acetylation [9] and infrared spectroscopy [8,10].

We tried unsuccessfully (up to date) to obtain suitable monocrystals of compounds **III** and **IV** in order to determine the crystal structure of them, but, fortunately, the crystal structure of one ester derived from **III** has been determined by us [11], consequently, we are able to do the unambiguous assignment of the epimers and the corresponding spectroscopic study of compounds **III** and **IV**.

Infrared Spectra.

The ir spectra of compounds **III** and **IV** in solid phase showed a strong band at 3353 and 3309 cm^{-1} respectively. These results indicate strong hydrogen bonding. Moreover, the relative low intensity of the Bohlmann bands in the 2800-2500 cm^{-1} region, as compared with those observed in other azabicyclic compounds [3], suggests that the lone pair of the nitrogen atom is implied in this bond (O-H...N).

NMR Spectra.

Spectral Analysis.

Assignments of proton resonances have been made on the basis of the literature data for α- and β-epimers of 3-phenetyl-3-azabicyclo[3.3.1]nonan-9-ol and related systems [1-3,12,13].

^1H NMR Spectra.

Overlapping resonance between different signals was observed for compounds **III** and **IV** in the solvents employed to record their ^1H nmr spectra (see Table 1).

Table 1

^1H NMR Chemical Shifts (δ, ppm) for Compounds III and IV [a]

Solvents	Deuteriochloroform		Perdeuteriobenzene	
	III	**IV**	**III**	**IV**
H7eq	1.34 dt	1.31 m	1.62 dt	1.19 dt
H6(8)eq	1.26 dd	1.57 m	1.68 m	1.64 ddt
H7ax	2.50 qt	2.48 m	2.55 qt	2.55 qt
H6(8) ax	1.60 tt	1.24 m	1.32 m	0.99 tdd
H1(5)	1.90 brs $W_{1/2}$~8	1.91 brs $W_{1/2}$~8	1.69 m	1.66 brs $W_{1/2}$~8
H2(4)ax, d	3.58	3.96	3.34	4.02
H9	4.15 t	4.07 t	3.74 q	3.56 t
$N-CH_3$, s	1.94	1.96	1.88	1.99
OH	1.60 s	1.57 s	1.0 d	0.98 s
C_6H_5 m	7.1-7.4 7.7-7.8	7.1-7.42 7.7-7.9	6.8-7.3 7.8-8	7-7.3 7.82-7.92

Abbreviations: br, broad; d, doublet; dd, doublet of doublets; ddt, doublet of doublets of triplets; dt, doublets of triplets; m, multiplet; qt, quartet of triplets; s, singlet; t, triplet. Error ± 0.05 ppm.

The signals due to $H2(4)_{ax}$ and H9 appear well differentiated.

In order to clarify the assignment of the signals and to deduce the proton magnetic parameters, double resonance experiments in deuteriochloroform and perdeuteriobenzene for **II** and **IV** were performed at 300 MHz.

^{13}C NMR Spectra.

The ^{13}C nmr chemical shifts and signal assignment of **III** and **IV** are listed in Table 3. These results are the same as those obtained by Jeyaraman *et al.* [7].

Table 2

^1H NMR Coupling Constants (J, Hz) for Compounds III and IV [a]

Solvents	Deuteriochloroform		Perdeuteriobenzene	
	III	**IV**	**III**	**IV**
H2(4)ax-H1(5)	3	3	3	3
H6(8)ax-H6(8)eq	-13.5	-12.5	-12.5	-13.5
H6(8)ax-H1(5)	4.5			3.5
H6(8)ax-H7ax	13.5	12	13.5	13
H6(8)ax-H7eq	5	5.5	4.5, 5.5	5.5
H9-H1(5)	3.4	3	3	3
H6(8)eq-H7ax	6	5.4	5.4	5.4
H6(8)eq-H7eq	<2	<2	<2	1.7
H6(8)eq-H1(5)	<2	1.9	<2	1.7
H7eq-H7ax	13	12	13.5	13
H9-OH				3

[a] Error ± 0.5 Hz except for the case where only a limit value was estimated taking into account the $W_{1/2}$ values.

Table 3

^{13}C Chemical Shifts (δ, ppm) for Compounds III and IV [a]

	III	**IV**
C1(5)	42.84	43.48
C2(4)	73.52	66.76
C6(8)	19.63	26.62
C7	20.50	20.59
C9	73.57	73.35
$N-CH_3$	44.10	43.99
Aromatic Carbons		
Ipso	143.01	143.54
Ortho	127.84 [b]	127.76 [b]
Meta	128.16	128.09
Para	126.58	126.35

[a] Directly measured on the spectra; error ± 0.05 ppm. [b] Broadned signal.

Conformational Study.

From the ^1H and ^{13}C nmr data of **III** and **IV**, the following general features for the bicyclic system were determined. These compounds adopt in deuteriochloroform and perdeuteriobenzene solutions a flattened chair-chair conformation. Cyclohexane ring is more flattened than the piperidine moiety. The $N-CH_3$ groups are in equatorial position.

These conclusions are supported by the following:

In the ^1H nmr spectra, the $W_{½}$ value for the H1(5) signals (~8 Hz) is in agreement with previously reported values for a flattened chair-chair conformation in related bicyclic systems [1-4,12,13]. For a boat disposition of one of these rings, the signal corresponding to H1(5) would be an unresolved doublet with a coupling constant about 18 Hz [14].

The ^3J H2(4)$_{ax}$-H1(5) ~3 Hz accounts for a dihedral angle about 60°. In compounds **III** and **IV**, ^3J H2(4)$_{ax}$-H1(5) is smaller than ^3J H6(8)$_{ax}$-H1(5), therefore, the dihedral angle H2(4)$_{ax}$-C-C-H1(5) is greater than H6(8)$_{ax}$-C-C-H1(5).

In all cases ^3J H6(8)$_{ax}$-H1(5) is greater than ^3J H6(8)$_{eq}$-H1(5) and ^3J H6(8)$_{ax}$-H7$_{eq}$ is greater than ^3J H6(8)$_{eq}$-H7$_{eq}$ consequently, the dihedral angles H6(8)$_{eq}$-C-C-H1(5) and H6(8)$_{eq}$-C-C-H7$_{eq}$ are greater than H6(8)$_{ax}$-C-C-H1(5) and H6(8)$_{ax}$-C-C-H7$_{eq}$ respectively.

The twin-chair conformation is unambiguously confirmed by the ^{13}C spectrum and its comparation with that of β-granatanol [15] and related systems [4,13,14]. Bearing in mind the similarity of the chemical shift of C7 for **III** and **IV** (Table 3) and the reported value for β-granatanol (19.8 ppm) it is clear that both compounds should adopt the same preferred conformation in solution, a flattened chair-chair form.

The N-CH$_3$ ^{13}C chemical shift of compounds **III** and **IV** of about 45 ppm is the same value as that found in equatorial N-CH$_3$ substituted piperidines [16].

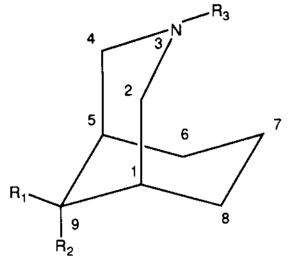
In compounds **III, IV**; Δδ H2(4)$_{ax}$[**IV**]-H2(4)$_{ax}$[**III**] ~ Δδ H6(8)$_{ax}$[**III**]-H6(8)$_{ax}$[**IV**] ~0.4 ppm was attributed to the field and steric effect exerted by the OH group on H2(4)$_{ax}$ and H6(8)$_{ax}$. In addition to that, in compounds **III** and **IV**, Δδ C2(4)[**III**]-C2(4)[**IV**] ~ Δδ C6(8)[**IV**]-C6(8)[**III**] ~7 ppm was attributed to the steric syn-diaxial effect exerted by the axial OH on H2(4)$_{ax}$ and H6(8)$_{ax}$; and to the increased eclipsing between H2(4)$_{ax}$ and H1(5), and H6(8)$_{ax}$ and H1(5).

In compounds **III, IV**; Δδ H7$_{ax}$[**III,IV**]-H7$_{eq}$[**III,IV**] ~1.2 ppm was attributed to the field effect exerted by the N lone pair on H7$_{ax}$. The Δδ H6(8)$_{eq}$[**IV**]-H6(8)$_{eq}$[**III**] = 0.3 ppm is attributed to the **W** arrangement of the equatorial protons with respect to the OH groups, consequently, these protons would be more sensitive to the OH inductive deshielding effect [17].

By comparing the δ ^{1}H and δ ^{13}C values of compounds **III** and **IV** with those of compounds **V** and **VI** (Scheme 2) [3], the following conclusions can be drawn:

The Δδ H7$_{ax}$[**III,IV**]-H7$_{ax}$[**V,VI**] ~0.6 ppm can be attributed to the π-effect exerted by the phenyl groups on H7$_{ax}$; in the same way the difference: Δδ H2(4)$_{ax}$-[**III**]-H2(4)$_{ax}$[**V**] ~1.4 ppm and Δδ H2(4)$_{ax}$[**IV**]-H2(4)$_{ax}$-[**VI**] ~1.4 ppm can be attributed not only to the σ-effect exerted by the phenyl groups on C2(4), but to the π-effect exerted by the phenyl groups on H2(4)$_{ax}$. Consequently, we propose for the phenyl groups a preferred conformation in which H2(4)$_{ax}$ are near coplanar with the phenyl groups. Also, the shape of the multiplets due to the δ H-aromatics in **III** and **IV** accounts for a distinct conformation of them (due to restricted phenyl spinning).

Scheme 2



Compound	R$_1$	R$_2$	R$_3$
V	H	OH	CH$_2$-CH$_2$-Ph
VI	OH	H	CH$_2$.CH$_2$-Ph

In summary, several strands of evidence establish that 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-α(β)-ols adopt in deuteriochloroform and perdeuteriobenzene solutions a flattened chair-chair conformation in which the cyclohexane ring is more flattened; this is due to the fact that in the flattening of the piperidine ring the phenyl groups would be shifted to endo positions in the bicyclic system, with the concomitant steric hindrance.

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