NMR Study of 1-Azatricyclo[3.3.1.1^{3,7}]decane Derivatives

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Received April 19, 1988

1-Azatricyclo[3.3.1.1^{3,7}]decan-4-one (4-oxo-1-azaadamantane) and 1-azatricyclo[3.3.1.1^{3,7}]decane-4-α-(β)-ol (4-α-(β)-hydroxy-1-azaadamantane) have been studied by ^{1}H and ^{13}C nmr methods. From this study several stereo and stereoelectronic effects have been deduced. The complete proton and carbon chemical shift assignments for the title compounds have been made, with the aid of two-dimensional nmr techniques.

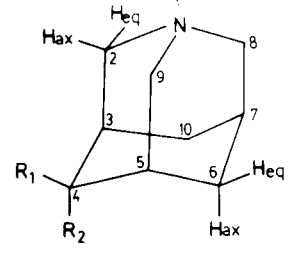
J. Heterocyclic Chem., **26**, 307 (1989).

Introduction.

The 1-azatricyclo[3.3.1.1^{3,7}]decane (1-azaadamantane) derivatives are compounds of great importance as conformationally rigid analogues of pharmacologlically active molecules and because of the increasing pharmacological interest of several 1-azaadamantane derivatives [1] [2] [3].

Due to the complexity of the 1-azaadamantane system, the ^{1}H and ^{13}C nmr literature data are not sufficiently detailed. In this paper compounds **I-III** (Scheme 1) have been studied in depth by ^{1}H nmr at 360 and 200 MHz and ^{13}C nmr at 90 and 50 MHz. The unequivocal assignment for all of the proton resonances of the 1-azaadamantane derivatives **I-III**, not described up to date, has also been carreied out.

Scheme 1



Compound	R_1	R_2
I	=O	
II	H	OH
III	OH	H

Hax and Heq are assigned with respect to piperidinol and cyclohexanol rings

Results and Discussion.

From the ^{13}C spectrum of the epimeric mixture of compounds **II** and **III** (the multiplicity of the carbon sites have been determined by means of a J modulated spin echo experiment [4]), and taking into account the value of $\Delta\delta C$ = 6 ppm, due to the syn-diaxial effect exerted by the OH group on the corresponding carbons in the piperidine and cyclohexane rings in related compounds [5-7], it can be unequivocally assigned the δ-values corresponding to C-2(9)**II**, C-2(9)**III**, C-6(10)**III** and C-6(10)**III**. The signals corresponding to C-4, C-3(5), C-7 and C-8 can be assigned taking into account the respective δ C-values in 4-oxo-1-azaadamantane [8], and related monoaza and diazabicyclic compounds [5-7], but it is not possible to determine to which epilmer belong each of these signals.

From the proton-carbon shift correlation spectrum of the epimeric mixture of **II** and **III** (Figure 1) and the corresponding ^{1}H-nmr spectrum (Figure 2) and keeping in mind the syn-diaxial deshielding anisotropic and steric effect exerted by the OH group on the corresponding H_{ax} protons in a condensed piperidine ring [5-7], the following assignments can be made: H-2(9)**II**, H-6(10)$_{ax}$**II**, H-6(10)$_{eq}$**II**, H-2(9)$_{eq}$**III**, H-2(9)$_{ax}$**III** and H-6(10)**III**.

By irradiation of the signal a 1.65 ppm, the unresolved triplet at 4.06 ppm collapses to a singlet and the W1/2 of the doublets at 2.88, 3.49 and 2.07 ppm become appreciably diminished. These facts confirm the assignment of H-4**III**, H-3(5)**III**, H-2(9)$_{eq}$**III**, H-2(9)$_{ax}$**III** and H-6(10)**III**.

On saturating the signal at 1.75 ppm, the unresolved triplet at 3.99 ppm collapses to a singlet, the doublet at 2.24 ppm collapses to a wide singlet and the W1/2 value of the doublets at 2.98 and 3.24 ppm becomes appreciably diminished. So, the assignments of H-4**II**, H-2(9)**II**, H-3(5)**II**, H-6(10)$_{ax}$**II** and H-6(10)$_{eq}$**II** are confirmed.

On saturating the signal at 3.49 ppm, the doublet at 2.88 ppm becomes to a singlet; this fact confirms the values of δ H-2(9)$_{ax}$**III** and δ H-2(9)$_{eq}$**III**.

The same irradiations were made in the spectrum in dimethyl sulfoxide-d_6 with analogous results.

The proton-proton shift correlation spectrum of the epimeric mixture **II** and **III** (Figure 3) leads finally to a complete assignment of the individual protons for both epimers. Thus, the following connectivities due to W arrangements: H-7**II** - H-3(5)**II**; H-7**III** - H-3(5)**III**; H-8**II** - H-2(9)$_{ax}$**II**, H-6(10)$_{ax}$**II** - H-2(9)$_{ax}$**II**; and H-8**III** - H-6(10)$_{ax}$-**III**, H-2(9)$_{ax}$**III** - H-6(10)$_{ax}$**III**, **allow the assignment of: H-7II**, H-7**III**, H-2(9)$_{ax}$**II** and H-6(10)$_{ax}$**III**, respectively.

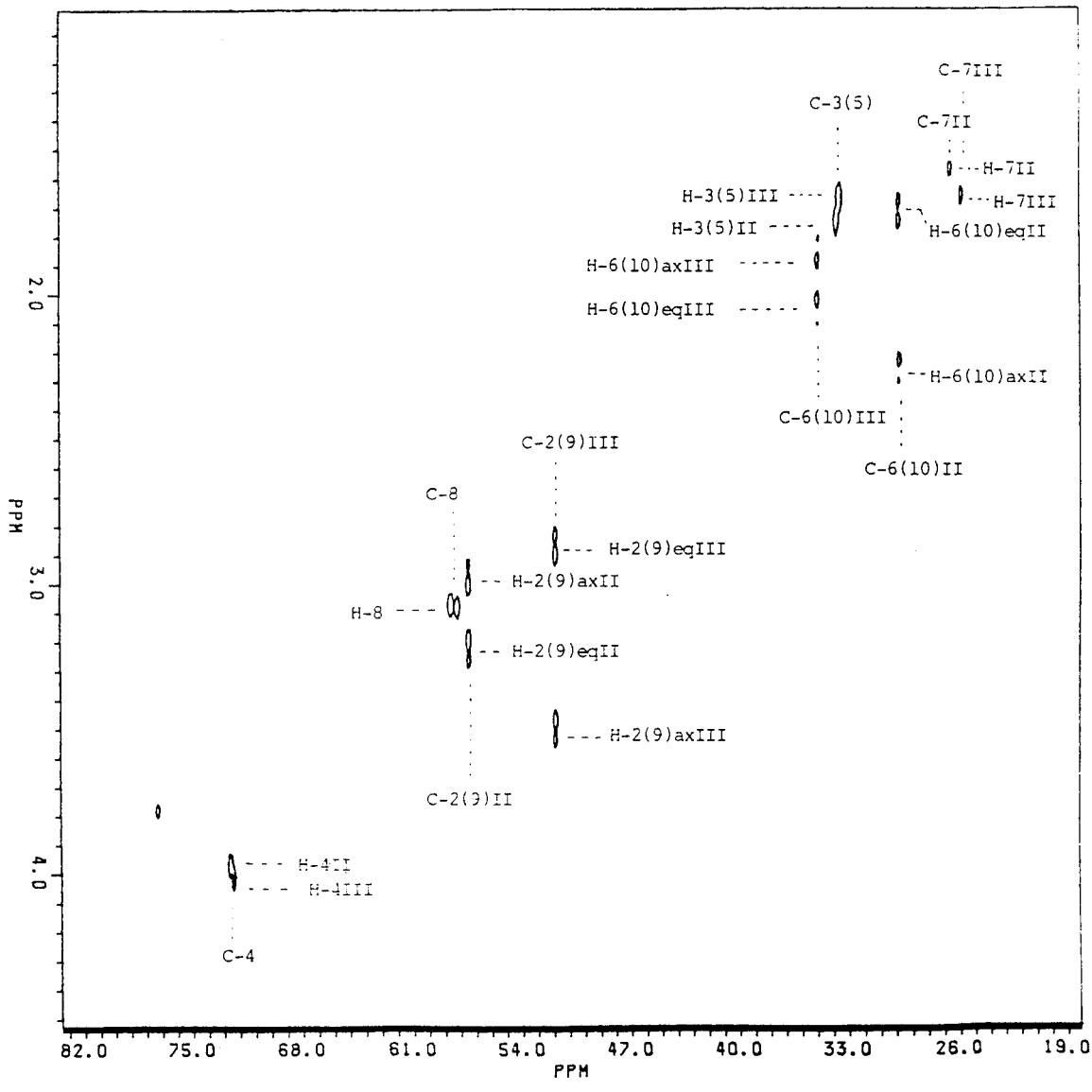


Figure 1. Proton-carbon shift correlation spectrum of **II** and **III**. The proton shifts are the ordinates and the carbon-13 shifts are the abscissae.

Table 1

^{1}H Chemical Shifts (δ, ppm) and Multiplicities (J, Hz) for Compounds **II** and **III**

Proton	$CDCl_3$ [a]	$(CD_3)_2SO$ [b]
2 (9) ax **III**	3.49 d ^2J 12.7	3.28 d ^2J 13.3
2 (9) eq **II**	3.24 d ^2J 12.8	3.02 d ^2J 13.3
2 (9) ax **II**	2.98 d	2.80 d
2 (9) eq **III**	2.88 d	2.66 d
3 (5) **II**	1.75 s	1.54 s
3 (5) **III**	1.65 s	1.46 brs
4 **III**	4.06 brs	3.82 brs
4 **II**	3.99 brs	3.76 brs
6 (10) ax **II**	2.24 d ^2J 12.2	2.16 d ^2J 11.4
6 (10) eq **III**	2.07 d ^2J 13.6	1.95 d ^2J 11.4
6 (10) ax **III**	1.86 d	1.76 d
6 (10) eq **II**	1.74 d	1.57 d
7 **III**	1.62 s	1.46 brs
7 **II**	1.56 s	1.46 brs
8 **II (III)**	3.08 s	2.89 s

[a] Spectra recorded (deuteriochloroform) at 360 and 200 MHz. [b] Spectra recorded (dimethyl sulfoxide-d_6) at 200 MHz. Abbreviations: br, broad; d, doublet; s, singlet.

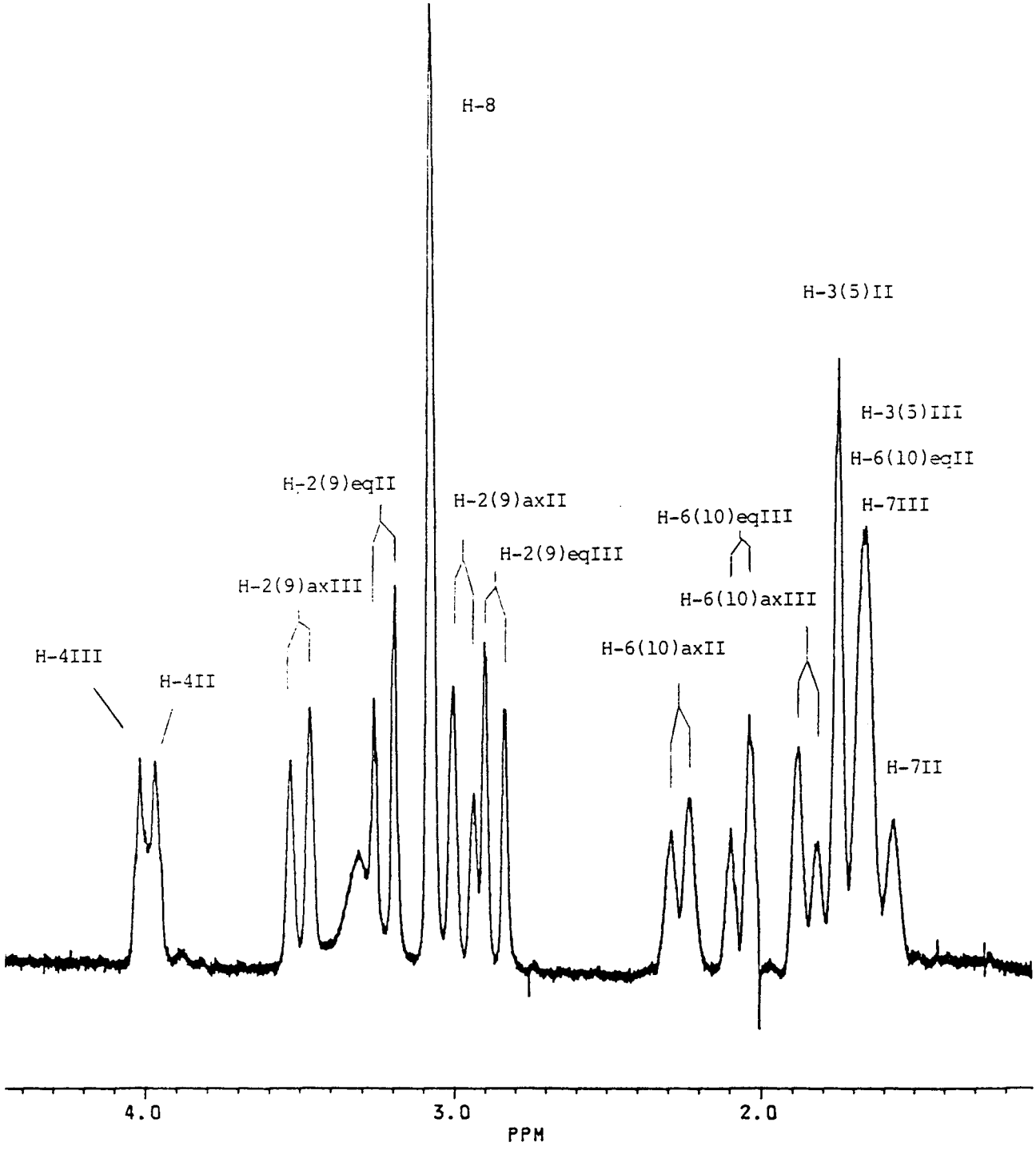


Figure 2. 200 MHz proton spectrum of compounds **II** and **III** in deuteriochloroform.

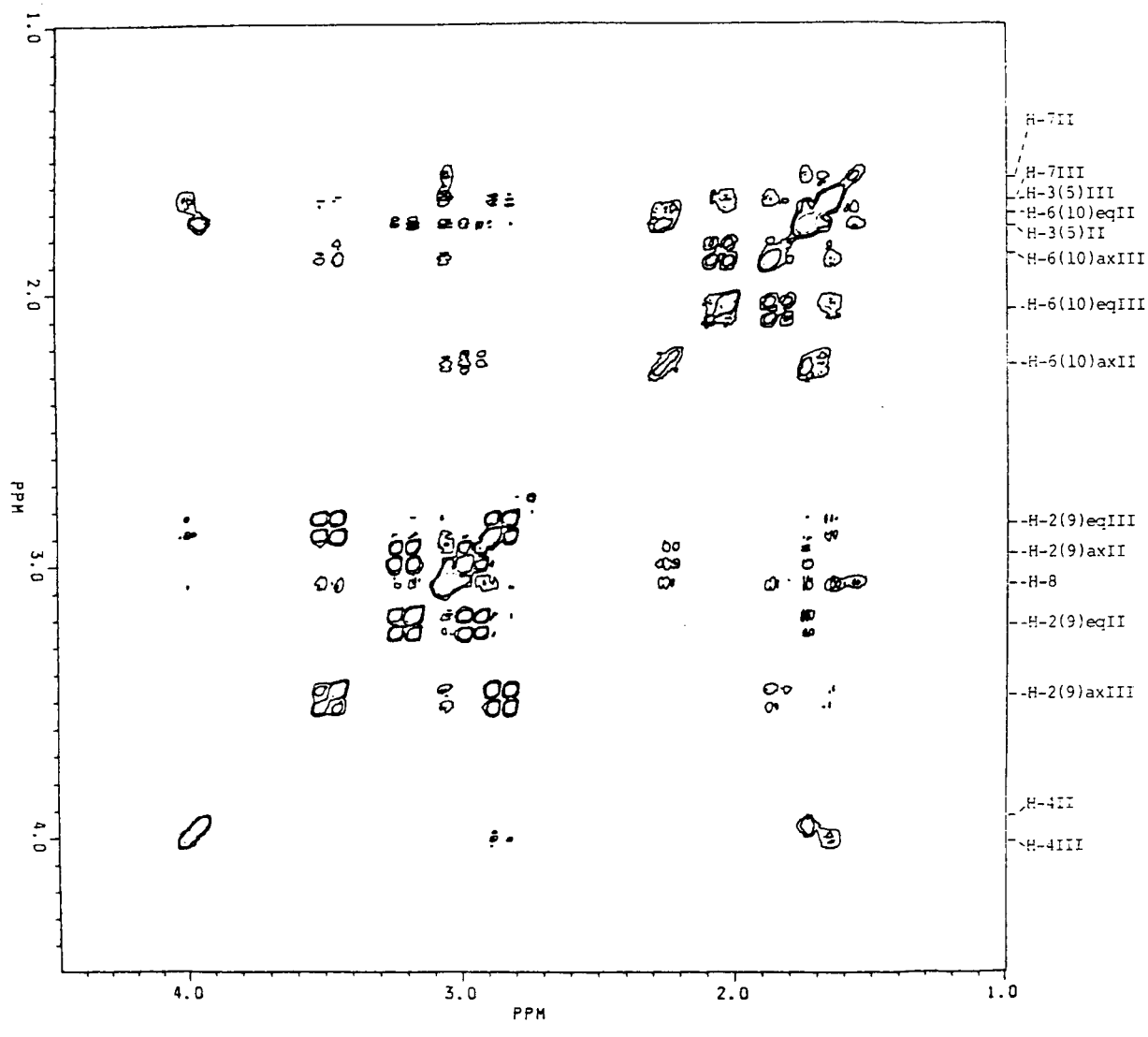


Figure 3. Contour plot of the 200 MHz proton COSY spectrum of **I** and **II** in deuteriochloroform.

Moreover, from the heteronuclear ^{1}H-^{13}C correlation spectrum (Figure 1) the assignments of the remaining δ C values of C-3(5)**II**, C-3(5)**III**, C-4**II**, C-4**III**, C-7**II** and C-7**III** can be made, once the resonances of the corresponding protons are known. However, because they overlap, a distinction between the δ C-8**II** and δ C-8**III** values, is not possible.

From the ^{1}H and ^{13}C nmr data (Tables 1 and 2) of compounds **II** and **III**, the following conclusions were obtained:

a) The $\Delta\delta$ C-2(9)**II** - δ C-2(9)**III** = 5.58 ppm and $\Delta\delta$ C-6(10)**III** - δ C-(10)**II** = 5.27 ppm is due to the aforementioned syn-diaxial effect, which is the same for the piperidinol and cyclohexanol rings of the 1-azaadamantane system.

b) The $\Delta\delta$ H-2(9)$_{ax}$**III** - δ H-2(9)$_{ax}$**II** = 0.51 ppm and $\Delta\delta$ H-6(10)$_{ax}$**II** - δ H-6(10)$_{ax}$**III** = 0.38 ppm are due to the

Table 2

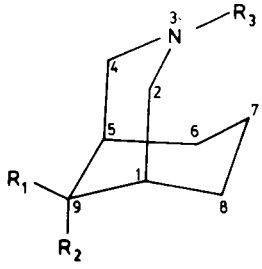
^{13}C Chemical Shifts (ppm) for Compounds **II** and **III** in deuteriochloroform at 50 MHz

C-2 (9) **II**	57.68
C-2 (9) **III**	52.10
C-3 (5) **II**	33.95
C-3 (5) **III**	33.75
C-4 **II**	72.91
C-4 **III**	72.82
C-6 (10) **III**	35.15
C-6 (10) **II**	29.88
C-7 **II**	26.72
C-7 **III**	26.00
C-8 **III** [a]	58.82
C-8 **II** [a]	58.47

[a] Assignments may be interchanged.

deshielding anisotropic and steric syn-diaxial effects exerted by the OH group. In the 3-phenethyl-3-azabicyclo-[3.3.1]nonan-9-α-(and β)-ols, **IV** and **V** (Scheme 2), the $\Delta\delta$ H-6(8)$_{ax}$**IV** - H-6(8)$_{ax}$**V** = 0.15 ppm [6] is due to the same effects; the difference between 0.38 and 0.15 ppm is due to the flexibility of the cyclohexane ring in the latter compounds, it is to say, we think that in compounds **II** and **III** the field and steric effects exerted by the OH group are very accurate values, due to the rigidity of the structure.

Scheme 2



Compound	R_1	R_2	R_3
IV	H	OH	CH_2CH_2Ph
V	OH	H	CH_2CH_2Ph

c) The $\Delta\delta$ H-2(9)$_{eq}$**II** - δ H-2(9)$_{eq}$**III** = 0.36 ppm and $\Delta\delta$ H-6(10)$_{eq}$**III** - δ H-6(10)$_{eq}$**II** = 0.33 ppm is tentatively attributed to the W arrangement of the equatorial protons with respect to the OH group, consequently, these protons would be more sensitive to the OH inductive deshielding effect. The differences $\Delta\delta$ H-2(9)$_{eq}$**II** - δ H-8**II** = 0.16 ppm and $\Delta\delta$ H-2(9)$_{eq}$**II** - δ H-2(9)$_{ax}$**II** = 0.26 ppm are explained in the same terms.

d) In compounds **IV** and **V** the $\Delta\delta$ H-6(8)$_{eq}$**V** - δ H-6(8)$_{eq}$**IV** = 0.09 ppm. The difference between 0.33 ppm [$\Delta\delta$ H-6(10)$_{eq}$**III** - δ H-6(10)$_{eq}$**II**] and 0.09 ppm is due to the flattening of the cyclohexane ring in compound **IV** [6].

The ^{1}H and ^{13}C nmr parameters of 4-oxo-1-azaadamantane are listed in Tables 3 and 4. The assignments have been carried out taking into account the δ values for **II** and **III**, and double resonance experiments.

Table 3

^{1}H Chemical Shifts (δ, ppm) and Multiplicities (J, Hz) for Compound **I**, in Deuteriochloroform at 360 MHz

H-2 (9) eq	3.40 d, ^{2}J 12.7
H-2 (9) ax	3.14 d
H-3 (5)	2.46 s
H-6 (10) eq	2.24 d, ^{2}J 11.9
H-6 (10) ax	2.09 d
H-7	1.72 s
H-8	3.21 s

Abbreviations: d, doublet; s, singlet.

Table 4

^{13}C Chemical Shifts (δ) and Coupling Constants (J, Hz) for Compound **I**, in Deuteriochloroform at 90 MHz

Carbon	δ (ppm)	^{1}J C-H (Hz) [a]
2 (9)	60.77	140.3
3(5)	47.90	139.1
4	214.31	
6 (10)	37.88	129.7
7	26.63	131.3
8	58.03	136.8

[a] Deduced from the proton coupled spectra.

EXPERIMENTAL

The ^{1}H and ^{13}C nmr spectra of compound I were recorded on a Bruker WM 360 spectrometer at 360 MHz and 90 MHz, respectively.

The nmr spectra of **II** and **III** were acquired using a Bruker AM 200 SY spectrometer equipped with an Aspect 3000 pulse-programmer. Frequency was 200.13 MHz for proton and 50.32 for ^{13}C. Conventional proton spectra were also recorded at 360 MHz.

The homonuclear chemical shift correlation 2D experiment [9,10] (program COSY. AU) was carried out by using the pulse sequence: $t_2 - 90°$-[^{1}H]-$t_1 - 45°$[^{1}H]-FID[^{1}H]. Pulses were phase cycled according to reference [11]. Recycle delay t_2 was 3s, the 90°[^{1}H] pulse was 7.5 μs. A total of 4 transients were collected for each t_1 values; number of increments 128; SW = 2SW1 = 701 Hz; number of points 1024. A sine bell window function was applied in both domains before zero filling twice in the F_1 domain.

Heteronuclear chemical shift correlated 2D spectra [12] (program XHCORR. AU) were obtained by using the pulse sequence: DO-$t_2 - 90°$-[^{1}H]$-\frac{1}{2}t_1 - 180°$[^{13}C]$-\frac{1}{2}t_1$-$\tau_1 - 90°$[^{1}H]$90°$[^{13}C]-τ_2-BB[^{1}H]-FID[^{13}C]. All pulses were phase cycled according to [11]. A 3s recycle delay was used and the delay times τ_1 and τ_2 were calculated from the compromise value $^1J_{CH}$ = 140 Hz. The 90°[^{1}H] pulse was 20 μs and the 90°[^{13}C] pulse was 7.5 μs. Carbon-13 spectral width was 3290 Hz and proton spectral width was 351 Hz; NT = 352; 128 t_1 increments were applied to characterize the ^{1}H domain and 1024 points characterized the ^{13}C domain. A sine bell window function was applied in both domains before zero filling in the proton domain.

Infrared spectra were obtained using a Perkin-Elmer 1310 spectrophotometer. Mass spectrum were recorded on a Hitachi-Perkin Elmer RMU-6M.

Synthesis.

4-Oxo-1-azaadamantane (**I**) was prepared according to the procedure reported by Black [13].

4-α(β)-Hydroxy-1-azaadamantanes **II**, **III**.

A solution of 4-oxo-1-azaadamantane (1.011 g, 6.7 mmoles) in dry tetrahydrofuran (20 ml) was added dropwise at room temperature under nitrogen to a stirred suspension of lithium aluminum hydride (628 mg, 16.6 mmoles) in the same solvent (25 ml). The mixture was heated under reflux for 1 hour, then cooled to 0°, hydrolyzed with the minimal amount of water and stirred at room temperature for 1 hour. The resulting suspension was diluted with dichlorometane (50 ml), filtered and the solid was washed several times with dichloromethane. The organic layer was separated, dried with anhydrous magnesium sulfate and evaporated

in vacuo to give a white solid that was purified by sublimation (130°, 2 torr); ir (potassium bromide): ν (cm^{-1}) 3600-2200, 1460, 1320, 1290, 1100; ms: m/e (relative intensity %): 153 (M^+, 69), 136 (36), 94 (35), 58 (100).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.53; H, 9.87; N, 9.15. Found: C, 70.34; H, 9.80; N, 9.26.

Acknowledgements.

The authors are indebted to Mrs. L. Lacombe (Collège de France, Paris) for recording two dimensional nmr spectra. We also thank Mr. A. Gómez Morilla (Instituto de Estructura de la Materia, C.S.I.C. Madrid) for recording 360 nmr spectra.

This research was supported by the Comision Asesora de Investigación Científica y Técnica (Grant 1750/82).

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