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APPLICATION OF 220 MHz NMR TO THE SOLUTION OF STEREOCHEMICAL PROBLEMS. III. AZASTEROIDS

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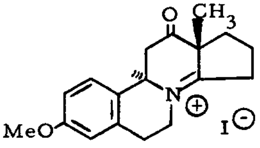
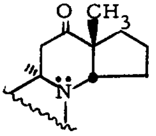
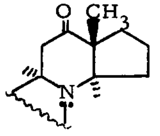
In the course of a study designed to totally synthesize 8- and 9-azasteroids, unique stereochemical problems arose, which due to the presence of nitrogen in the molecule, could not be resolved by comparison with homocyclic steroid models. The 12-ketoiminium salt (I)[3] upon reduction by hydride reagents or catalytic means, produced a mixture of two components, one of which (II) was identified by direct comparison[4] with the known 12-desoxy derivative. The other component, expected to be IV, did not coincide with the known 12-desoxy derivative.[4]



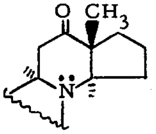
I



II



III



IV

Since there was no known derivative corresponding to III, it became a formidable task to determine whether the C-14 proton was α or β. That the lone pair on nitrogen was α was confirmed by infrared[5] and nmr[6] techniques. The β orientation of the C-18 protons were also readily assigned by the 60 MHz spectrum in benzene and chloroform.[7] However, the C-14 proton was not discernible in either the 60 or 100 MHz spectrum since the C-6, C-7 and C-11 protons resonate in the same region. Examination of the 220 MHz spectrum[8] of III (Figure 1) allowed a first order assignment of the configuration at C-14. The broad pattern at δ 2.67 with splittings of 11 and 7 Hz is assigned the 14-H by comparison with its deuteriated analog. These splittings are consistent with dihedral angles expected for the axially oriented 14α-H (Table I). A further examination of models would indicate a similar splitting pattern for the C-14 proton in the β position. However, comparison of the 220 MHz spectrum of II, known to possess a

BC-cis fusion, the C-14 proton is β-oriented and resonates at δ2.60 (Table I). The similarity of the chemical shifts for the C-14 protons in II and III suggest very similar magnetic environments for these protons. Since the 14β-H is cis to the lone pair in II, it is reasonable to assume that 14α-H is also cis to the lone pair in III. It should be noted that the 14-H in III cannot be cis to the lone pair if it possessed a β-orientation. It is therefore concluded that 14-H in III, discernible only at 220 MHz, can be assigned an α-orientation and the CD ring in III is trans fused. A complete assignment of all protons in II and III was made and recorded in Table I.

It is of further interest that these assignments confirm that the electrons are released from the iminium bond toward the same side as the incoming hydride ion. This is contrary to what has been observed for the 17-keto-8-azaiminium salts.[3c,4] This behavior will be discussed more fully in a future report.

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8. The NMR spectral data were obtained by running five to six $CDCl_3$ solutions of the two isomers (II and III) on a Varian HR-220 superconducting spectrometer.

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TABLE I

220 MHz SPECTRAL DATA

II			III		
Proton	(ppm)	J	Proton	(ppm)	J
6β (a)	3.02	6α6β (gem) = 16.00	6α (a)	2.97	6α6β (gem) = 17.5
		6β7α (aa) = 12.00	6β (e)	2.48	6β7β (ea) = 3.50
		6β7β (ae) = 5.00			6β7α (ee) = 3.50
6α (e)	2.64	6α7α (ea) = 3.25			
		6α7β (ee) = 2.00			
7β (e)	3.23	7α7β (gem) = 12.00	7α (e)	3.22 ± 0.05	
7α (a)	2.21		7β (a)	3.22 ± 0.05	
8 e^- β (a)	---		8 e^- α (e)	---	
9α (a)	3.85	9α11β (aa) = 11.00	9α (a)	4.65	9α11β (aa) = 7.00
		9α11α (ae) = 4.25			9α11α (ae) = 1.75
11β (a)	2.54	11α11β (gem) = 17.00	11α (e)	2.91	11α11β (gem) = 15.00
11α (e)	3.08		11β (a)	3.14	
14β	2.60	14β15α (ea) = 5.00 ± 1	14α	2.67	14α15β = 11.00
		14β15β (ee) = 5.00 ± 1			14α15α = 7.00
18β	1.22		18β	1.20	
CH_3O	3.78		CH_3O	3.72	

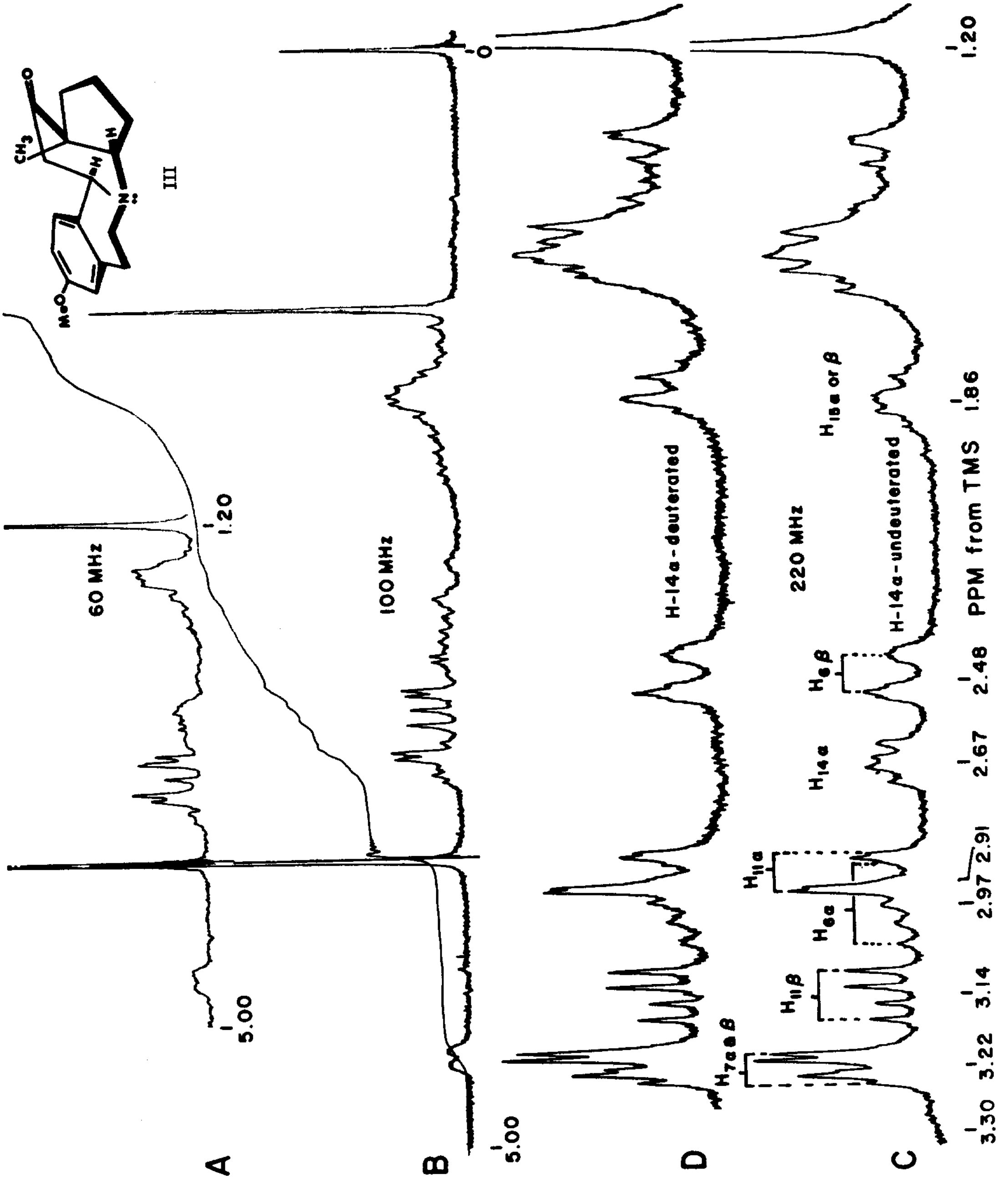
MeO
CH3
O
H
H
III
A
B
D
C
60 MHz
100 MHz
220 MHz
H-14α-deuterated
H-14α-undeuterated
5.00
1.20
5.00
0
H7αβ
H11β
H6α
H11α
H14α
H6β
H15α or β
3.30
3.22
3.14
2.97
2.91
2.67
2.48
1.86
1.20
PPM from TMS

FIGURE 1