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CONFORMATIONS OF 2,4-SUBSTITUTED 9-METHYL-9-AZA-3-OXABICYCLO[3.3.1]NONAN-7-ONES

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Bicyclo[3.3.1.]nonane system provides interesting conformational problems. The molecules usually adopt preferentially the double-chair rather than the boat-chair conformation.[1)] However, relative stability between these conformations is also associated with the introduction of functional groups[2)] and/or hetero-atoms into the framework.[3,4)] In connection with synthetic studies of laurencin,[5)] we prepared several entitled compounds and examined their conformations (and hence configurations). The present paper describes the result, which indicates that all the compounds exist in the double-chair conformation, irrespective of the presence of 2,4-diaxial substituents.

The examined compounds (I ~ VIII),[6)] listed in Table 1, were prepared newly, except 2,4-unsubstituted compound (I),[7)] by the Robinson-Schöpf condensation of 2,4-dialkyl-3-oxaglutaraldehydes[8)] with methylamine and acetonedicarboxylic acid.

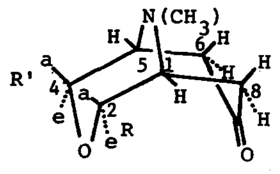

Table 1 9-Methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-ones

	R (C_2)	R' (C_4)		R (C_2)	R' (C_4)
I	H	H	V	β-C_2H_5	α-C_2H_5
II	β-$AcOCH_2$	H	VI	β-$AcOCH_2$	β-C_2H_5
III	α-$AcOCH_2$	H	VII	β-$AcOCH_2$	α-C_2H_5
IV	β-C_2H_5	β-C_2H_5	VIII	α-$AcOCH_2$	β-C_2H_5

The conformations were elucidated on the basis of the NMR spectra, exemplified by Fig. 1; the chemical shifts and coupling constants were estimated by comparison with those of analogous compounds[4b,4d)] as well as by extensive spin decoupling studies. The summarized result (Table 2) is completely consistent with the double-chair conformation for all compounds, though the conformations of N-methyl group were not assigned. The conclusive evidence was presented by the X-ray crystallography of compound VI.

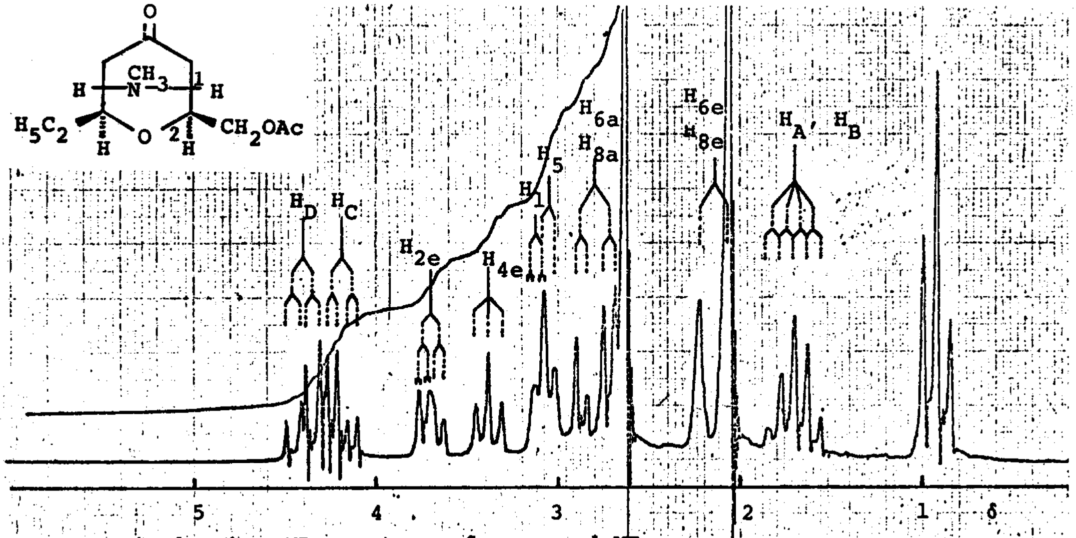

Fig.1 The NMR spectrum of compound VII

The crystals are triclinic, with two molecules in a unit cell with the dimensions of a = 8.660(2), b = 9.615(2), c = 8.816(2) Å, α = 72.28(2)°, β = 98.99(3)°, and γ = 97.85(2)°. The space group is P$\bar{1}$. Intensities of 2360 unique reflections with 2θ values up to 140° were measured on an automatic, four-circle diffractometer using CuKα radiation monochromatized with a LiF crystal. The structure was solved by the direct method[9] on the basis of 465 |E| values above 1.30, and was refined by the block-diagonal-matrix least-squares method with anisotropic temperature factors for all the

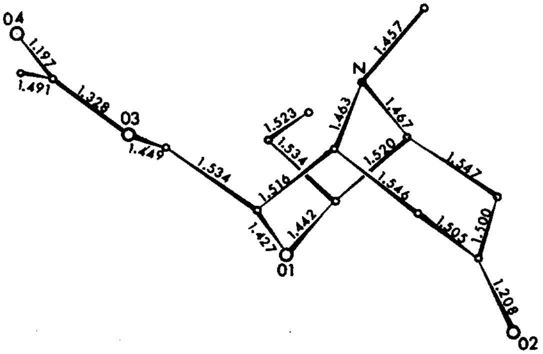

Fig. 2 The molecular conformation and the bond distances (Å) of compound VI.

Table 2. The NMR spectra of 9-methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-ones[a,b,c)]

Compounds	Chemical sifts $(\delta)^{d,e)}$ and Coupling constants $(J)^{f,g)}$													
	$\underline{H}_1$	$\underline{H}_5$	$\underline{H}_{2e}$	$\underline{H}_{4e}$	$\underline{H}_{2a}$	$\underline{H}_{4a}$	$\underline{H}_{6e}$	$\underline{H}_{8e}$	$\underline{H}_{6a}$	$\underline{H}_{8a}$	$CH_3C\underline{H}_A\underline{H}_B$		$AcOC\underline{H}_C\underline{H}_D$	
I	3.10	3.10	3.70	3.70	3.83	3.83	2.24	2.24	2.70	2.70	—		—	
	$\underline{3.00}$	$\underline{3.00}$	$\underline{3.62}$	$\underline{3.62}$	$\underline{3.71}$	$\underline{3.71}$	$\underline{2.12}$	$\underline{2.12}$	$\underline{2.61}$	$\underline{2.61}$	—		—	
	br d,	br d,	d,	d,	br d,	br d,	d,	d,	do d,	do d,	—		—	
II	3.08	3.08	3.80	3.51	—	4.03	2.20	2.20	2.53	2.78	—		4.68	4.23
	br d,	br d,	do d,	d,	—	br d,	d,	d,	do d,	do d,	—		do d,	do d
III	3.10	3.10	—	3.78	3.98	3.89	2.16	2.24	2.72	2.61	—		3.98	
	br d,	br d,	—	br d,	m,	br d,	br d,	br d,	do d,	do d,	—		br s	
IV	$\underline{2.82}$	$\underline{2.82}$	$\underline{3.00}$	$\underline{3.00}$	—	—	$\underline{1.92}$	$\underline{1.92}$	$\underline{2.51}$	$\underline{2.51}$	$\underline{1.62}$	$\underline{1.60}$	—	
	br d,	br d,	do t,	do t,	—	—	d,	d,	do d,	do d,	quin,	quin	—	
V	$\underline{2.76}$	$\underline{2.76}$	$\underline{3.36}$	—	—	$\underline{3.57}$	$\underline{1.96}$	$\underline{2.04}$	$\underline{2.55}$	$\underline{2.30}$	$\underline{1.40}$		—	
	br d,	br d,	do d,	—	—	do do d,	d,	d,	do d,	do d,	complex m		—	
VI	3.12	3.06	3.69	3.39	—	—	2.18	2.18	2.80	2.80	1.70		4.38	4.18
	br d,	d,	br do d,	t,	—	—	d,	d,	do d,	do d,	quin,		do d,	do d
VII	3.06	2.99	3.83	—	—	3.80	2.23	2.17	2.55	2.74	1.38		4.69	4.22
	br d,	m,	br do d,	—	—	br m,	d,	d,	do d,	do d,	complex m,		do d,	do d
VIII	3.10	3.04	—	3.56	4.00	—	2.19	2.19	2.75	2.55	1.58		4.00	
	br d,	br d,	—	do d,	m,	—	d,	d,	do d,	do d,	complex m,		br s	

	$J_{1,2e}$	$J_{5,4e}$	$J_{1,2a}$	$J_{5,4a}$	$J_{1,8e}$	$J_{5,6e}$	$J_{1,8a}$	$J_{5,6a}$	$J_{2,H}$		$J_{4,H}$	
I	0.0	0.0	1.0	1.0	0.0	0.0	6.0	6.0	—		—	
II	0.0	0.0	—	2.0	0.0	0.0	6.0	6.0	8.0	5.0	—	
III	—	0.5	0.5	1.0	0.0	0.0	6.0	6.0	small		—	
IV	2.0	2.0	—	—	0.0	0.0	6.0	6.0	6.5	6.5	6.5	6.5
V	0.0	—	—	2.0	0.0	0.0	6.0	4.0	8	6	9	5
VI	1.5	0.0	—	—	0.0	0.0	6.0	6.0	7	7	8	5
VII	0.5	—	—	1.0	0.5	1.5	6.0	6.0	8	6	?	
VIII	—	0.5	1.0	—	0.0	0.0	6.0	6.0	small		8	6

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a) The spectra were measured in $CDCl_3$ at 100 MHz with a JEOL High Resolution NMR spectrometer, model JNM-PS-100. b) The abbreviations "br, d, do, s, m, and quin" mean "broad, doublet, double, singlet, multiplet, and quintet," respectively, and "H_{2e} and H_A" refer to "equatorial proton at C_2 and one of ethyl methylene protons." c) The abbreviations "$J_{1,2e}$ and $J_{2,H}$" refer to "coupling constants between H_1 and H_{2e} and between one of H_{2e} and H_{2a} and one of H_A to H_D. d) The underlined δ values denote chemical shifts in CCl_4. e) The chemical shifts of N-CH_3 (singlet), acetoxyl methyl (singlet) and ethyl methyl protons (triplet with J = 6.5-7.0 Hz) fell within δ 2.49 ~ 2.61, 2.02 ~ 2.05, and 0.85 ~ 0.93, respectively. f) The coupling constants were estimated by first-order approximations. g) The coupling constants, $J_{2a,2e}$ (I), $J_{4a,4e}$ (I to III), $J_{6a,6e}$ (I to VIII), $J_{8a,8e}$ (I to VIII) and J_{CD} (II, VI and VII) were estimated to be 11.5, 11 ~ 11.5, 15 ~ 16, 15 ~ 16, and 11 Hz, respectively.

non-hydrogen atoms. Since a difference Fourier map yielded the locations of all the twenty-one hydrogen atoms, further least-squares refinement including these hydrogen atoms was carried out. The final R value was 5.7%. The molecular framework thus obtained is shown in Fig. 2.

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