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Stereochemical Studies on 7-Substituted 8-Oxa-1-azabicyclo[4.3.0]nonanes.

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A set of racemic 7-substituted 8-oxa-1-azabicyclo[4.3.0]nonanes have been prepared and configurational and conformational assignments made on the basis of the value of the geminal coupling constants for the C_9 methylene protons. The limitations of the Bohlmann infrared criterion in studying the conformations of these compounds is discussed.

The importance of J_{GEM} (1) in studying the conformations of 8-oxa-1-azabicyclo[4.3.0]nonanes with methyl substituents in the six-membered ring has been demonstrated (2). The results, describing the variation of J_{GEM} with conformation, are here applied to the problem of assigning configurations to a series of racemic 7-substituted 8-oxa-1-azabicyclo[4.3.0]nonanes.

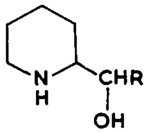
The 7-substituted compounds were prepared by the action of formaldehyde on the corresponding piperidyl carbinols (I) and in each case the two possible racemic epimers II and III were isolated.

Assuming each epimer to be undergoing rapid interconversion between the possible *cis*- and *trans*-fused ring conformations the n.m.r. spectra obtained will be that corresponding to the average conformation. From a consideration of Dreiding models, it can be seen that the *cis*-fused ring conformations of III (IIIb and IIIc) are relatively free of serious non-bonded interactions compared with those occurring in the analogous conformations (IIb and IIc) of II. It would, therefore, be expected that the average conformation of II would approximate more closely to the *trans*-fused ring conformation than would the average conformation of III which should possess an appreciable contribution from the *cis*-fused ring conformation.

It has been shown (2) that 8-oxa-1-azabicyclo-[4.3.0]nonanes existing in predominantly *trans*-fused ring conformations show a J_{GEM} of -0.8 c.p.s. whereas those in predominantly *cis*-fused ring conformations show a J_{GEM} of -5 c.p.s. 8-Oxa-1-azabicyclo[4.3.0]nonane shows a J_{GEM} of -2.4 c.p.s. indicating the presence of an appreciable amount of the *cis*-fused ring conformation in equilibrium with the *trans*-fused ring conformation. Thus, epimer II should show a more positive J_{GEM} than epimer III.

From a consideration of the n.m.r. spectra of the racemic epimers (Table I) the compounds fall naturally into two groups, the members of a group showing similar values for J_{GEM} and for the difference in chemical shift between the C_9 methylene protons ($\Delta_{H_9H_9'}$).

In the light of the above discussion, configuration II has been assigned to the group of racemic epimers having a J_{GEM} of between -1.2 and -1.3 c.p.s. since a J_{GEM} of this magnitude indicates a predominantly *trans*-fused ring conformation. Similarly those epimers having a J_{GEM} of between -2.1 and -2.7 c.p.s. correspond to configuration III. $\Delta_{H_9H_9'}$ is smaller for epimer III than for epimer II and this is in accord with the chemical shift data (3) on the methyl substituted 8-oxa-1-azabicyclo[4.3.0]-nonanes where $\Delta_{H_9H_9'}$ for the predominantly *trans*-fused ring conformations is ~0.85 p.p.m. and for the predominantly *cis*-fused ring conformations is ~0.16 p.p.m. To add support to the above argument, the n.m.r. spectrum of III (R = Et) was run



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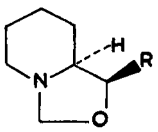

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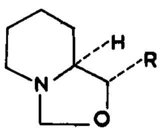

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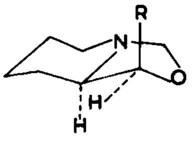

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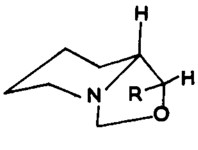

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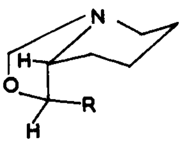

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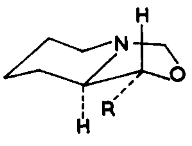

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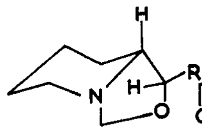

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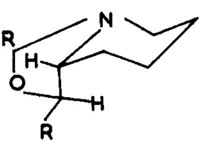


IIIc

TABLE I

N.m.r. Spectra of 7-Substituted 8-oxa-1-azabicyclo[4.3.0]nonanes

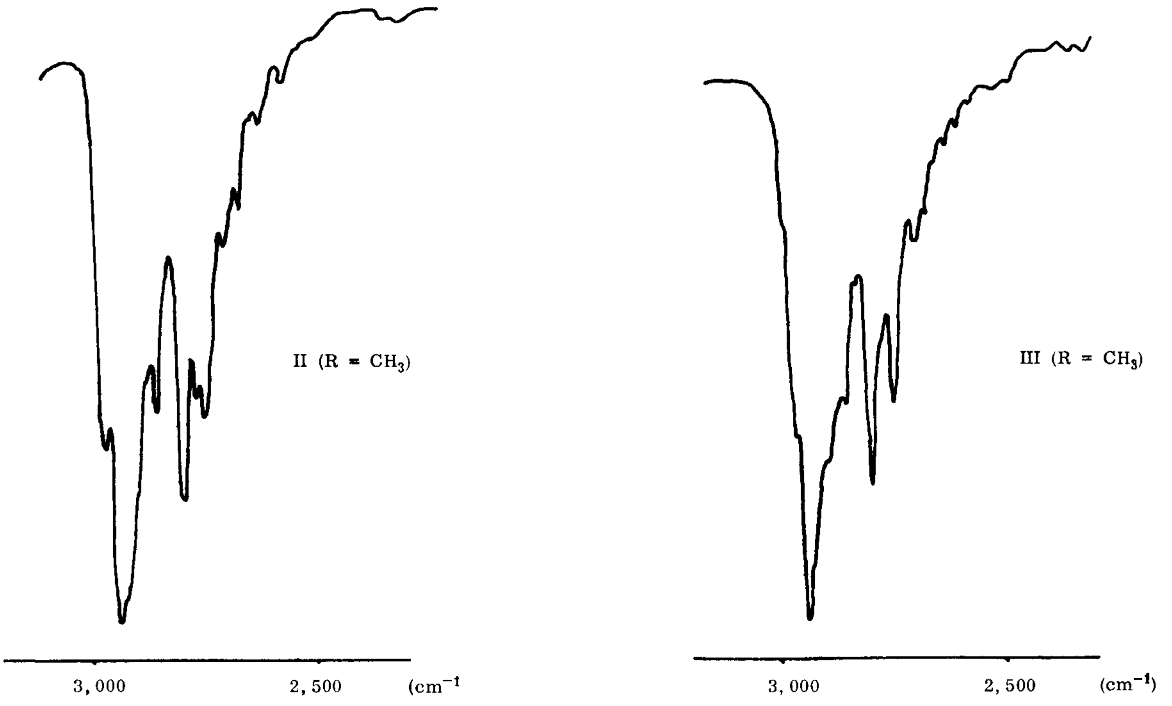
Compound	m.p. picrate	C_9 protons	Chemical Shifts (τ) Centres of multiplets C_2 and C_6 protons H_{eq}	H_{ax}	$\Delta_{H_9H_9'}$ (p.p.m.)	J_{GEM} (c.p.s.)
III (R = CH_3-)	172°	5.62 6.15	7.03, 7.21	7.85	0.53	-2.4
III (R = CH_3CH_2-)	149°	5.60 6.19	7.04, 7.22	7.9	0.59	-2.1
III (R = $(CH_3)_2CH$-)	164°	5.61 6.23	7.17	7.63	0.62	-2.1
III (R = C_6H_5-)	156-157°	5.36 5.79	7.08	7.68	0.43	-2.7
II (R = CH_3-)	154-155°	5.49 6.37	6.91, 7.08	8.0	0.88	-1.2
II (R = CH_3CH_2-)	137°	5.58 6.42	7.0, 7.14	8.0	0.84	-1.3
II (R = $(CH_3)_2CH$-)	168-169°	5.51 6.28	6.96, 7.11	8.0	0.77	-1.2
II (R = C_6H_5-)	172-173°	5.30 6.22	6.92, 7.08	7.9	0.92	-1.3
7,7'-Dimethyl 8-oxa-1-azabicyclo[4.3.0]nonane	152-153°	5.54 6.36	6.96, 7.11	8.15	0.82	-1.0
7,7'-Diphenyl 8-oxa-1-azabicyclo[4.3.0]nonane	115-117°	5.16 6.09	6.90, 7.06	7.95	0.93	-1.5

TABLE II

Infrared Spectra of 7-Substituted 8-oxa-1-azabicyclo[4.3.0]nonanes

Compound	Cm^{-1}	ϵ_A	Cm^{-1}	ϵ_A	Cm^{-1}	ϵ_A	Cm^{-1}	ϵ_A	Cm^{-1}	ϵ_A
III (R = CH_3-)	2942	268.8	2860	146.2	2800	154.9	2752	114.6	2700	51.2
	2680	42.2	2667	30.2	2635	22.8	2610	20.5		
III (R = CH_3CH_2-)	2940	276.4	2880	163.9	2858	141.0	2800	154.9	2752	122.0
	2700	65.3	2680	56.8	2635	32.8	2615	32.8		
III (R = $(CH_3)_2CH$-)	2948	276.4	2885	137.9	2867	129.8	2820	80.6	2808	93.5
	2760	62.4	2715	40.5	2690	30.2	2640	20.5		
III (R = C_6H_5-)	2938	239.6	2870	96.8	2850	94.2	2828	51.9	2794	123.7
	2765	57.3	2752	68.9	2700	31.2	2675	26.9	2627	18.8
II (R = CH_3-)	2938	265.3	2855	118.8	2797	160.4	2770	112.4	2754	118.8
	2710	58.0	2688	47.4	2678	47.4	2635	25.1	2580	15.2
II (R = CH_3CH_2-)	2940	276.4	2880	93.5	2858	90.2	2800	133.8	2775	96.8
	2750	96.8	2737	96.8	2714	48.4	2695	42.2	2670	37.7
II (R = $(CH_3)_2CH$-)	2937	292.5	2870	142.0	2857	150.5	2799	100.3	2770	74.3
	2747	77.5	2722	51.2	2675	32.8				
II (R = C_6H_5-)	2944	234.2	2860	90.2	2800	173.4	2773	110.9	2753	103.8
	2712	48.4	2680	42.2	2663	30.2	2637	27.7		
7,7'-Dimethyl 8-oxa-1-azabicyclo[4.3.0]nonane	2938	240.7	2853	77.5	2788	150.5	2744	103.8	1697	51.2
	2677	45.8	2630	27.7						
7,7'-Diphenyl 8-oxa-1-azabicyclo[4.3.0]nonane	2942	240.7	2860	103.8	2796	175.8	2762	103.8	2750	103.8
	2700	45.8	2680	40.5	2638	25.4	2617	18.1		

Infrared Spectra of II (R = CH_3) and III (R = CH_3)



at low temperatures in carbon disulphide solution (7). At 0°, $\Delta_{H_9H_9'}$ = 0.6 p.p.m. and J_{GEM} = -2.1 c.p.s. and at -95°, $\Delta_{H_9H_9'}$ = 0.7 p.p.m. and J_{GEM} = -1.5 c.p.s.

Some of the most useful information regarding the stereochemistry of compounds possessing bridgehead nitrogen has been obtained from infrared spectra. Bohlmann (4) has shown that quinolizidines in which there are at least two C-H bonds adjacent to nitrogen orientated axially and *trans* to the nitrogen lone pair show strong bands in the 2700 - 2800 cm^{-1} region. The applicability of the Bohlmann correlation to indolizidines (5) and certain oxa-azabicyclic systems (3, 6) has been demonstrated.

All the compounds in the present study show strong Bohlmann bands in the infrared (Table II) and comparison of the infrared spectra of II (R = CH_3) and III (R = CH_3) illustrates the small differences in the appearance of these bands which is observed for a pair of racemic epimers. However, if some rough linear relationship exists between pure *trans* (J_{GEM} ≅ 1 c.p.s.) and pure *cis* (J_{GEM} ≅ 5 c.p.s.), then the value for III (J_{GEM} ≅ 2.5 c.p.s.) would indicate 40-50% of the *cis*-conformation as being present in the equilibrium mixture. Thus in this particular set of compounds the Bohlmann correlation appears to be of limited applicability since, although compounds III show strong Bohlmann bands, the systems could still only be about 50-60% in the *trans*-conformation.

Additional confirmation of the correctness of these assignments is the fact that II, (R = Et) was prepared from *dl*-conhydrine; the absolute configuration of conhydrine having been determined (8, 9). For purposes of comparison 7, 7'-dimethyl and 7, 7'-diphenyl 8-oxa-1-azabicyclo[4.3.0]nonane were synthesized and, as seen from Table I, these both exist in predominantly *trans*-fused ring conformations as evidenced by the values for J_{GEM} of -1 c.p.s. and -1.5 c.p.s. respectively.

EXPERIMENTAL

All elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Microanalytical Laboratory, Bonn, Germany. Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237 grating instrument and measured as 0.2 *M* solutions in carbon tetrachloride using 0.1 mm. matched cells. The n.m.r. spectra were determined on a Perkin-Elmer R.10 spectrometer as 10% solutions in carbon tetrachloride with tetramethylsilane as internal reference.

Preparation of Substituted 8-oxa-1-azabicyclo[4.3.0]nonanes - General Procedure.

The substituted 2-piperidyl carbinol was shaken with an excess of 36% formaldehyde solution for half an hour. The mixture was basified with aqueous sodium hydroxide solution and extracted three times with ether. The ether was dried (sodium sulfate), evaporated, and the residue distilled to give the 7-substituted 8-oxa-1-azabicyclo[4.3.0]nonane.

7-Methyl 8-Oxa-1-azabicyclo[4.3.0]nonane.

α-Methyl-2-piperidylcarbinol (10) (20 g.) on treatment with formaldehyde gave a mixture of II (R = Me) and III (R = Me) (14.2 g., 65%) as a colourless oil, b.p. 73-75°/18 mm. This formal (10 g.) was converted to the picrate and after fractional recrystallization from ethanol the pure picrate (9.0 g.) of epimer III of 7-methyl-8-oxa-1-azabicyclo[4.3.0]nonane was obtained as yellow needles, m.p. 171-172° (Found: C, 44.91; H, 4.74; N, 14.85. $C_{14}H_{18}N_4O_8$ requires: C, 45.41; H, 4.86; N, 15.17). Concentration of the mother liquors yielded first a mixture of the epimeric picrates (10 g.) and finally the impure picrate of epimer II. On recrystallization from ethanol the pure picrate (7.0 g.) of epimer II of 7-methyl-8-oxa-1-azabicyclo[4.3.0]nonane was obtained as yellow needles, m.p. 154-155° (Found: C, 45.30; H, 4.73; N, 15.15. $C_{14}H_{18}N_4O_8$ requires: C, 45.41; H, 4.86; N, 15.17).

The picrate of epimer III (9.0 g.) was decomposed with cold aqueous sodium hydroxide solution and immediately ether extracted (sodium sulfate). Concentration and distillation yielded epimer III of 7-methyl-8-oxa-1-azabicyclo[4.3.0]nonane (2.8 g., 82%) as a colourless oil $n_D^{20.5}$ 1.4555 b.p., 109-110°/22 mm. (Found: C, 68.23; H, 10.76; N, 9.82. $C_8H_{15}NO$ requires: C, 68.08; H, 10.62; N, 9.93).

The picrate of epimer II (7.0 g.) was decomposed and worked up as before to give epimer II of 7-methyl-8-oxa-1-azabicyclo[4.3.0]nonane (1.75 g., 66%) as a colourless oil $n_D^{23.0}$ 1.4532, b.p. 114-116°/29 mm. (Found: C, 67.83; H, 10.87; N, 9.98. $C_8H_{15}NO$ requires: C, 68.08; H, 10.62; N, 9.93).

7-Ethyl-8-oxa-1-azabicyclo[4.3.0]nonane.

Epimer II was obtained (7.3 g., 85%) as a colourless oil $n_D^{20.0}$ 1.4708, b.p. 95°/17 mm. by the action of formaldehyde on *dl*-conhydrine (11) (Found: C, 69.59; H, 11.07; N, 9.22. $C_9H_{17}NO$ requires: C, 69.63; H, 11.04; N, 9.02). The picrate formed yellow needles, m.p. 137° from ethanol (Found: C, 45.84; H, 5.33; N, 14.59. $C_{15}H_{20}N_4O_8$ requires: C, 46.87; H, 5.25; N, 14.58).

Epimer III was obtained as a colourless oil $n_D^{20.0}$ 1.4664, b.p. 98°/17 mm. by the action of formaldehyde on the α-ethyl-2-piperidylcarbinol (11) having a m.p., 71° (Found: C, 69.14; H, 10.95; N, 9.06. $C_9H_{17}NO$ requires: C, 69.63; H, 11.04; N, 9.02). The picrate formed dark yellow needles from ethanol, m.p. 149° (Found: C, 46.52; H, 4.95; N, 14.62. $C_{15}H_{20}N_4O_8$ requires: C, 46.87; H, 5.25; N, 14.58).

7-Isopropyl-8-oxa-1-azabicyclo[4.3.0]nonane.

An epimeric mixture of II (R = $(CH_3)_2CH$-) and III (R = $(CH_3)_2CH$-) was obtained (7.0 g.) as a colourless oil, b.p. 61-63°/17 mm. (Found: C, 69.59; H, 11.43; N, 8.28. $C_{10}H_{19}NO$ requires: C, 70.96; H, 11.32; N, 8.28). The formal (7.0 g.) was converted to the picrate and fractional recrystallization from ethanol yielded the pure picrate of epimer II of 7-isopropyl-8-oxa-1-azabicyclo[4.3.0]nonane (4.1 g.) as yellow needles, m.p. 168-169° (Found: C, 47.97; H, 5.48; N, 13.98. $C_{16}H_{22}N_4O_8$ requires: C, 48.24; H, 5.57; N, 14.07).

Concentration of the mother liquors yielded impure picrate of epimer III. Fractional recrystallization then gave the pure picrate of epimer III of 7-isopropyl-8-oxa-1-azabicyclo[4.3.0]nonane (7.5 g.) as yellow needles, m.p. 164° from ethanol (Found: C, 48.50; H, 5.54; N, 13.93. $C_{16}H_{22}N_4O_8$ requires: C, 48.24; H, 5.57; N, 14.07). The picrate of epimer II (4.1 g.) was decomposed with aqueous sodium hydroxide solution to give epimer II of 7-isopropyl-8-oxa-1-azabicyclo-[4.3.0]nonane (1.2 g., 70%) as a very low melting point white solid, b.p. 56-58°/3 mm. Decomposition of the picrate of epimer III as above yielded 2.3 g. (72%) of epimer III of 7-isopropyl-8-oxa-1-azabicyclo[4.3.0]nonane as a colourless oil $n_D^{20.5}$ 1.4690, b.p. 62-63°/15 mm.

7-Phenyl-8-oxa-1-azabicyclo[4.3.0]nonane.

Epimer II was obtained by the action of formaldehyde on the α-phenyl-2-piperidylcarbinol (12) m.p., 140-141° and was a white crystalline solid, m.p. 43-44° from ether (Found: C, 77.25; H, 8.16; N, 6.98. $C_{13}H_{17}NO$ requires: C, 76.84; H, 8.37; N, 6.89). The picrate formed dark yellow plates, m.p. 172-173° from ethanol (Found: C, 52.44; H, 4.65; N, 13.19. $C_{19}H_{20}N_4O_8$ requires: C, 52.77; H, 4.66; N, 12.96).

Epimer III was obtained by the action of formaldehyde on the α-phenyl-2-piperidylcarbinol (12) m.p., 170-171° as a colourless oil $n_D^{20.5}$ 1.5436, b.p. 120-122°/1.7 mm. (Found: C, 77.35; H, 8.57; N, 7.02. $C_{13}H_{17}NO$ requires: C, 76.84; H, 8.37; N, 6.89). The picrate formed yellow needles, m.p. 156-157° from ethanol (Found: C, 52.88; H, 4.30; N, 13.15. $C_{19}H_{20}N_4O_8$ requires: C, 52.77; H, 4.66; N, 12.96).

7, 7'-Dimethyl-8-oxa-1-azabicyclo[4.3.0]nonane was obtained as a colourless oil $n_D^{20.5}$ 1.4617, b.p. 43-44°/0.45 mm. (Found: C, 69.72; H, 11.17; N, 9.05. $C_9H_{17}NO$ requires: C, 69.68; H, 10.97; N, 9.03). The picrate formed yellow needles, m.p. 152-153° from ethanol (Found: C, 46.92; H, 5.06; N, 14.67. $C_{15}H_{20}N_4O_8$ requires: C, 46.87; H, 5.25; N, 14.58).

7, 7'-Diphenyl-8-oxa-1-azabicyclo[4.3.0]nonane was obtained as a white crystalline solid, m.p. 116-118° (Lit. (13) 117-121°) from ether. The picrate formed yellow needles, m.p. 115-117° from ethanol (Found: C, 58.78; H, 4.92; N, 10.77. $C_{25}H_{24}N_4O_8$ requires: C, 59.05; H, 4.76; N, 11.02).

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(1) Throughout this paper J_{GEM} refers to the geminal coupling for the C_9 methylene protons and is assumed to be negative.

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