

SATURATED HETEROCYCLES, PART 31.¹ SYNTHESIS AND CONFORMATIONAL STUDIES
OF 2-OXO- AND 2-THIOTETRAHYDRO-1,3-OXAZINES WITH CONDENSED SKELETONS

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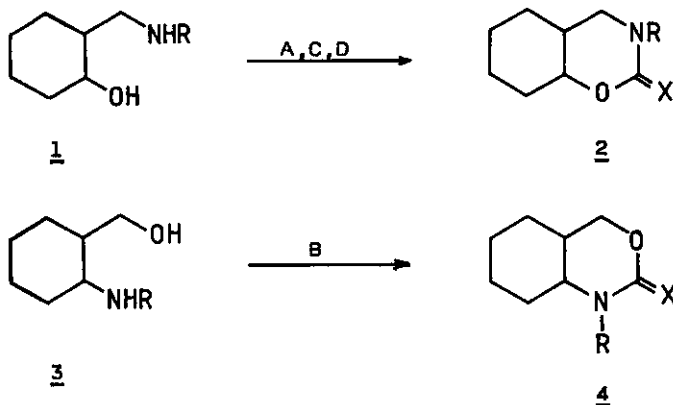
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Abstract - Stereoisomeric 2-oxo- and 2-thio-4,5- (and 5,6)-tetra-methylenetetrahydro-1,3-oxazines (2 and 4) have been synthesized. ¹H nmr spectra afford evidence that in the case of the cis isomers of derivatives 2, prepared from 2-(aminomethyl)cyclohexanols, the O-inside conformer predominates, independently of the N-substituent (R = H, CH₃); in derivatives 4, made from 2-(hydroxymethyl)cyclohexylamines, the N-inside conformer predominates if R = H, while the N-outside conformer does so when R = CH₃.

We have reported the syntheses² and stereochemical study³ of tetra-methylene- and pentamethylenetetrahydro-1,3-oxazin-2-ones. This work has now been extended to N-methyl-substituted tetramethylenetetrahydro-1,3-oxazin-2-ones and the corresponding 2-thiones.

The starting amino alcohols 1 and 3 were prepared by methods reported by us.^{4,5} From these, the tetrahydro-1,3-oxazin-2-ones 2 and 4 were synthesized by the method of Mousseeron and co-workers⁶ using urea (Method A), and by the sodium methoxide cyclization of the ester prepared by reaction with ethyl chloroformate (Method B). The thio derivatives, 2e-h, were obtained as described by Menard and co-workers⁷, the dithiocarbamates of the amino alcohols being prepared by their reaction with carbon disulfide followed by cyclization (Method C), or by reaction of the N-methylamino alcohols with thiophosgene (Method D).



R = H, CH₃; X = O, S

A: (H₂N)₂CO; C: CS₂/OH⁻; D: Cl₂CS; B: ClCO₂Et/MeONa

Two (N- or O-inside and N- or O-outside) chair-chair conformers are possible in the cis isomers of compounds 2 and 4, whereas the trans isomers have a single chair-chair conformer.

Determination of the conformation of the cis isomers is based on the ¹H nmr data of the corresponding cis-trans isomer pairs. In all compounds, the bridgehead protons and the heterocyclic methylene protons form an ABMX spin system; comparison of their parameters (Table 1) permits the unequivocal determination of the conformations. For convenience, Table 1 also includes the data of four compounds (2a,b and 4a,b) reported earlier³. It is seen that the nature of the substituent X (O or S) does not have an appreciable influence on the ¹H nmr data.

The H_M and H_X bridgehead protons are naturally axial in the trans compounds, and consequently the system is characterized by two diaxial coupling constants (J_{AM}, J_{MX}) and an axial-equatorial interaction (J_{BM}). Owing to the two diaxial couplings, the H_X signal of the trans compounds is very broad, the half-height width being 20-25 Hz. For the cis isomers 2a and 4a the width of the H_X signal is less than 10 Hz; at the same time, its chemical shift is higher by 0.5 ppm than that for the corresponding trans isomers. This suggests that the H_X atom is equatorial in these compounds, as in the analogous heterocycles

No.	Configuration	R	X	mp °C	Method	¹ H nmr data in CDCl ₃ (δ _{TMS} =0 ppm) at 60 MHz									
						δ _{H_A} ^d (ppm)	δ _{H_B} ^d (ppm)	$\frac{J_{AB}}{\nu}$ ^d (Hz)	$\frac{J_{AM}}{\nu}$ ^d (Hz)	$\frac{J_{BM}}{\nu}$ ^d (Hz)	δ _{H_X} (ppm) m(1H)	Δ ^g δ _{H_X} (Hz)	δ _{NH_f} or δ _{NCH₃} (ppm) g(1H or 3H)	δ _{CH₂} ^g δ _{CH₉} (ppm) m(9H)	
<u>2a</u> ^a	<u>cis</u>	H	O		A	3.42	3.06	12	4	4	4.45	8	~7.0	1.2-2.2	
<u>2b</u> ^a	<u>trans</u>	H	O		A	2.95	3.30	12	11	5	3.87	25	~7.0	0.8-2.5	
<u>2c</u>	<u>cis</u>	CH ₃	O	81-83	A	3.59	2.94	10	6	2	4.50	8	3.00	0.8-2.5	
<u>2d</u>	<u>trans</u>	CH ₃	O	76-77	A	3.15			g ^b		3.85	24	3.00	0.8-2.5	
<u>2e</u> ^c	<u>cis</u>	H	S	144-146	C	3.50	3.10	12	5	3	4.50	8	~8.8	1.5-3.5	
<u>2f</u> ^c	<u>trans</u>	H	S	260-262	C	3.55	2.90	14	12	6	3.85	21	~8.7	1.5-3.3	
<u>2g</u> ^c	<u>cis</u>	CH ₃	S	69-70	D	3.61	3.05	14	6	2	4.50	10	3.45	1.2-2.3	
<u>2h</u> ^c	<u>trans</u>	CH ₃	S	157-159	D	~3.35					~3.9	24	3.45	0.8-2.5	
<u>4a</u> ^a	<u>cis</u>	H	O		A	4.22	4.11	12	2.5	2.5	3.65	10	~7.2	1.2-2.2	
<u>4b</u> ^a	<u>trans</u>	H	O		A	3.90	4.17	10.5	11.5	4	2.98	21	~7.1	0.8-2.3	
<u>4c</u>	<u>cis</u>	CH ₃	O	bp _{2mm} 160	B	4.39	4.11	10	10	4.5	3.30	~25	3.00	1.0-2.0	
<u>4d</u>	<u>trans</u>	CH ₃	O	bp _{2mm} 140	B	3.90	4.10	10	10	5	~3.0	~25	2.98	1.0-2.4	

^aPrepared² and spectroscopically studied³ by us earlier. ^b($\frac{J_{AM} + J_{BM}}{2}$). ^c1r (in KBr): No band in the region 1800-1600 cm⁻¹. The highest frequency of the NCSO group is at 1550 (2e), 1560 (2f) or 1510 cm⁻¹ (2g,h). ^dν_{C=O}: 2e 1685, 2b 1685, 2c 1680, 2d 1670, 4a 1690, 4b 1685, 4c 1665, 4d 1680 cm⁻¹. ^eFrom the AB part of the ABX multiplet. ^fHalf-band width of the X signal. ^gBroad signal. ^hBroad multiplet of the cyclohexyl protons 5, 7, 8, 9, 10.

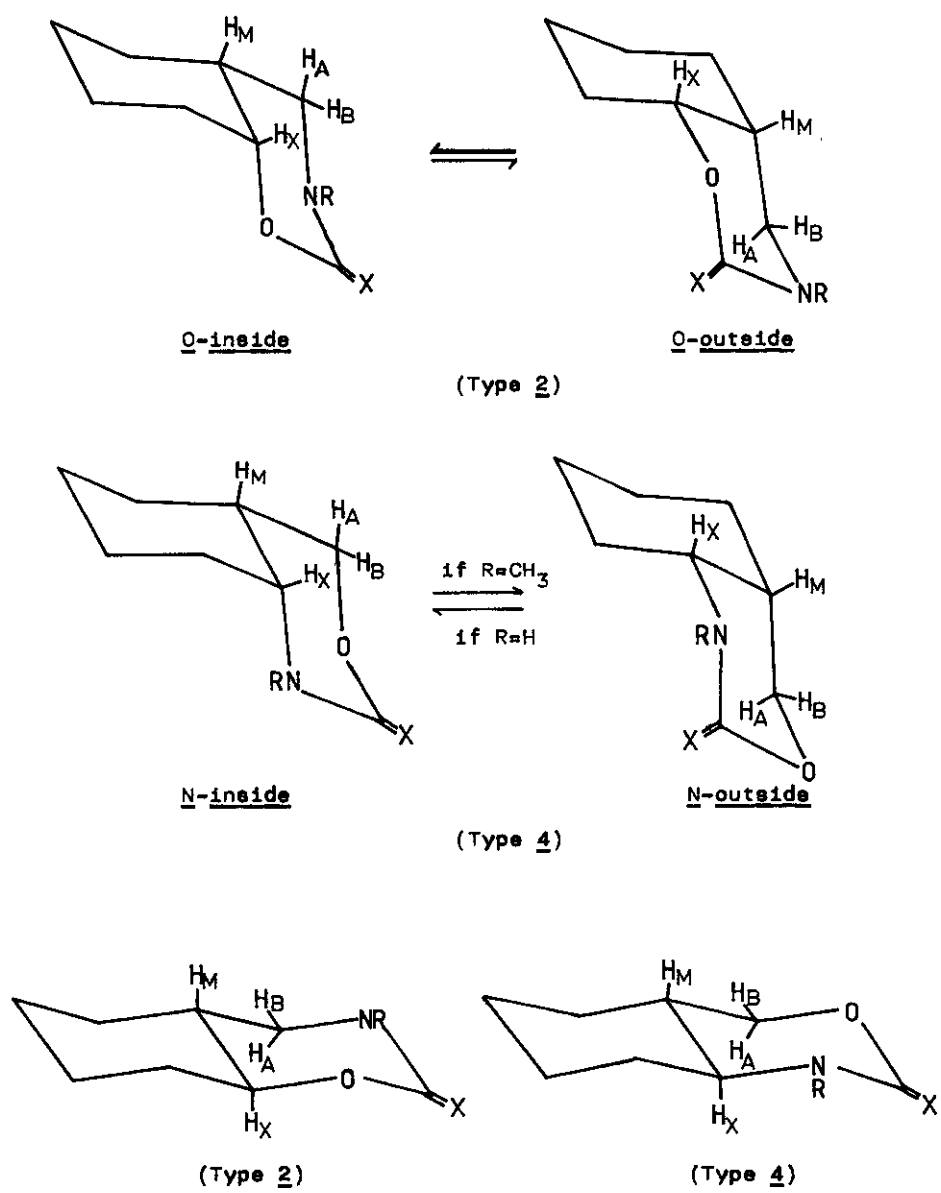


Fig. 1

investigated by us earlier.^{2,3,8} This means that the N- (or O-) inside form is predominant. In accordance with this, the J_{AM} and J_{BM} coupling constants show the diequatorial and equatorial-axial mutual positions of the AM and BM proton pairs, respectively, in relation to the hetero ring; this is possible if the compound has N- (or O-) inside conformation.

In contrast to the above, in the case of the N-methyl cis derivative (4c), the width of the H_X signal is similar to that in the trans derivatives (~ 25 Hz); on the other hand, the chemical shift is somewhat higher than for the corresponding trans isomer, but lower by 0.35 ppm than for the cis isomer 4a having N-inside conformation. All these facts show that the N-outside conformer is predominant in 4c, i.e. when the N-CH₃ group is directly bonded to the cyclohexane ring. In accordance, the spectrum of 4c indicates the diaxial and equatorial-axial nature of the AM and of the BM interactions, respectively.

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