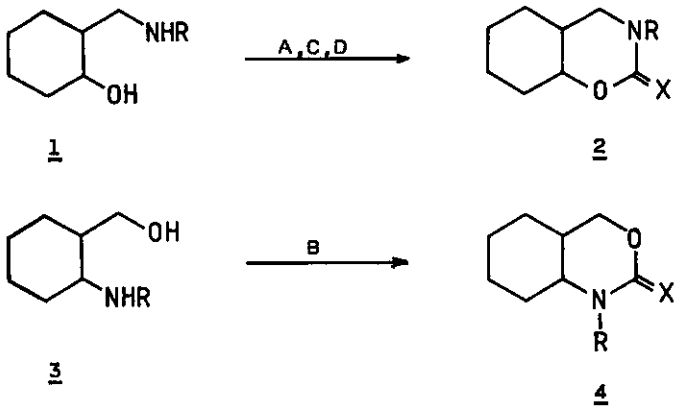
SATURATED HETEROCYCLES, PART 31.[1] SYNTHESIS AND CONFORMATIONAL STUDIES OF 2-OXO- AND 2-THIOTETRAHYDRO-1,3-OXAZINES WITH CONDENSED SKELETONS

Géza Stájer, Angela E. Szabó, Ferenc Fülöp and Gábor Bernáth*
Institute of Pharmaceutical Chemistry, University Medical School Szeged, POB 121, H-6701 Szeged, Hungary
and
Pál Sohár
EGYT Pharmacochemical Works, POB 100, H-1475 Budapest, Hungary

Abstract - Stereoisomeric 2-oxo- and 2-thio-4,5- (and 5,6)-tetramethylenetetrahydro-1,3-oxazines (2 and 4) have been synthesized. ^{1}H 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, CH_3); 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 = CH_3.

We have reported the syntheses[2] and stereochemical study[3] of tetramethylene- 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 Mousseron and co-workers[6] using urea (Method A), and by the sodium methoxide cyclization of the ester prepared by reaction with ethyl chloroformate (Method B). The thio derivatives, 2a-h, were obtained as described by Menard and co-workers[7], 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).



1 2

3 4

R = H, CH_3; X = O, S

A: $(H_2N)_2CO$; C: CS_2/OH^-; D: Cl_2CS; B: $ClCO_2Et/MeONa$

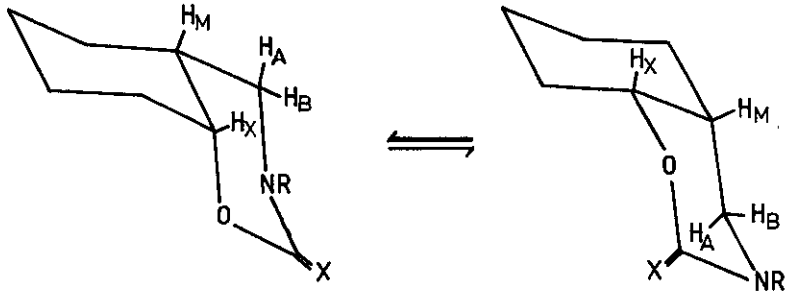
Two (N- or O-inside and N- or O-outside) chair-chair conformers are possible in the cis isomers of compounds 2 and 4, whereas the trans isomers have a single chair-chair conformer.

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 earlier[3]. 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

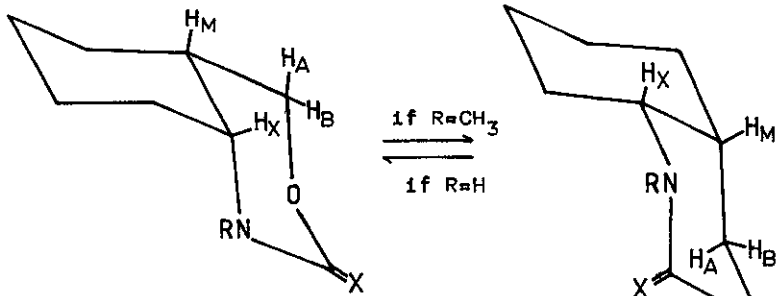
No.	Configuration	R	X	mp °C	Method	^{1}H nmr data in $CDCl_3$ (δ_{TMS}=0 ppm) at 60 MHz								
						δH_A[d] (ppm)	δH_B[d] (ppm)	J_{AB}[d] (Hz)	J_{AM}[d] (Hz)	J_{BM}[d] (Hz)	δH_X (ppm) m(1H)	$\Delta\nu H_X$[e] (Hz)	δ NH[f] or δNCH_3 (ppm) s(1H or 3H)	δCH_2[g] δCH[g] (ppm) m(9H)
2a[a]	cis	H	O		A	3.42	3.06	12	4	4	4.45	8	~7.0	1.2-2.2
2b[a]	trans	H	O		A	2.95	3.30	12	11	5	3.87	25	~7.0	0.8-2.5
2c	cis	CH_3	O	81-83	A	3.59	2.94	10	6	2	4.50	8	3.00	0.8-2.5
2d	trans	CH_3	O	76-77	A	3.15			8[b]		3.85	24	3.00	0.8-2.5
2e[c]	cis	H	S	144-146	C	3.50	3.10	12	5	3	4.50	8	~8.8	1.5-3.5
2f[c]	trans	H	S	260-262	C	3.55	2.90	14	12	6	3.85	21	~8.7	1.5-3.3
2g[c]	cis	CH_3	S	69-70	D	3.61	3.05	14	6	2	4.50	10	3.45	1.2-2.3
2h[c]	trans	CH_3	S	157-159	D	~3.35					~3.9	24	3.45	0.8-2.5
4a[a]	cis	H	O		A	4.22	4.11	12	2.5	2.5	3.65	10	~7.2	1.2-2.2
4b[a]	trans	H	O		A	3.90	4.17	10.5	11.5	4	2.98	21	~7.1	0.8-2.3
4c	cis	CH_3	O	bp_{2mm} 160	B	4.39	4.11	10	10	4.5	3.30	~25	3.00	1.0-2.0
4d	trans	CH_3	O	bp_{2mm} 140	B	3.90	4.10	10	10	5	~3.0	~25	2.98	1.0-2.4

[a]Prepared[2] and spectroscopically studied[3] by us earlier. [b]$(J_{AM} + J_{BM})/2$. [c]ir (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). ν C=O: 2a 1685, 2b 1685, 2c 1680, 2d 1670, 4a 1690, 4b 1685, 4c 1665, 4d 1680 cm^{-1}. [d]From the AB part of the ABMX multiplet. [e]Half-band width of the X signal. [f]Broad signal. [g]Overlapped multiplet of the cyclohexyl protons 5, 7, 8, 9, 10.



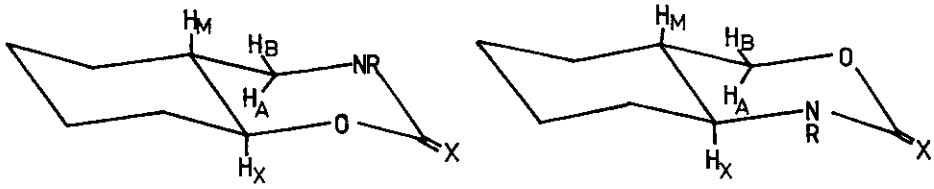
O-ineide O-outeide

(Type 2)



N-ineide N-outside

(Type 4)



(Type 2) (Type 4)

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 ($\sim$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-CH_3 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.

REFERENCES

1. Part 51/30: G. Tóth, F. Fülöp, F. Bernáth, I. Hermecz, K. Simon and Z. Mészáros: J.C.S. Perkin I, in press; this forms Stereochemical Studies, Part 52.
2. G. Bernáth, Gy. Göndös, K. Kovács and P. Sohár: Tetrahedron, 1973, 29, 981.
3. P. Sohár and G. Bernáth: Org. Magnetic Resonance, 1973, 5, 159.
4. G. Bernáth, K. Kovács and K. L. Láng: Acta Chim. Acad. Sci. Hung., 1970, 64, 183.
5. L. Gera, G. Bernáth and P. Sohár: Acta Chim. Acad. Sci. Hung., 1980, 105, 293.
6. M. Mousseron, F. Winternitz and M. Mousseron-Canet: Bull. Soc. Chim. France, 1953, 737.
7. M. Menard, A. M. Wrigley and F. L. Chubb: Can. J. Chem., 1961, 39, 273.
8. G. Bernáth, F. Fülöp, L. Gera, L. Hackler, A. Kálmán, Gy. Argay and P. Sohár: Tetrahedron, 1979, 35, 799.

Received, 17th December, 1981