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STEREOCHEMICAL STUDIES 130
SATURATED HETEROCYCLES 132[1]

SYNTHESIS AND RING-CHAIN TAUTOMERISM OF STEREOISOMERIC 1,3-OXAZINES CONDENSED WITH THE CYCLOPENTANE RING[1]

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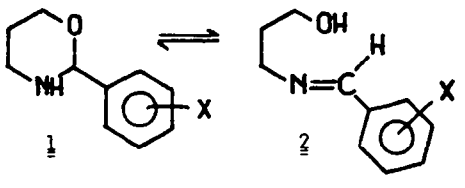
Abstract - Through condensation of cis-2-hydroxymethylcyclopentylamine (3) and cis-2-aminomethylcyclopentanol (5) with aromatic aldehydes, tautomeric mixtures of 1,3-oxazines and open-chain Schiff bases were obtained. The two series of compounds (4a-f, 6a-f) gave satisfactory linear correlations corresponding to $\log K_X = k\sigma^+ + \log K_{X=H}$ ($k = 0.76 \pm 0.04$ as shown earlier[2]). The ring form of the corresponding trans derivatives is present in a fairly low amount, because of the strain in the trans fusion of the cyclopentane and the six-membered hetero ring. N-Methyl substitution makes the ring form in the latter compounds stable, resulting in oxazines 12 and 14. All the cyclizations in question occurred stereospecifically.

The ring-chain tautomerism of tetrahydro-1,3-oxazines and 1,3-oxazolidines is a well-known process.[2-3] The tautomerism of oxazolidines has been thoroughly investigated, since the ring formation is a disfavoured 5-endo-trig process according to the Baldwin rules,[4-8] but for the 1,3-oxazine series quantitative data on the tautomeric ratios are available only for 3,4-dihydro-2H-1,3-benzoxazines.[9]



1 2

A comparative study was recently carried out on the ring-chain tautomerism of seven different series of 2-aryl-substituted tetrahydro-1,3-oxazines: tetrahydro-1,3-oxazines (1), (r-8a,c-2,c-4a)- and (r-8a,c-2,t-4a)-1,3-perhydrobenzoxazines, (r-8a,c-2,c-4a)- and (r-8a,c-2,t-4a)-3,1-perhydrobenzoxazines, 3,4-dihydro-2H-1,3-benzoxazines and 1,2-dihydro-4H-3,1-benzoxazines.[2] For all seven series, the following equation is valid:

$$\log K_X = (0.76 \pm 0.04)\sigma^+ + \log K_{X=H} \qquad (1)$$

where $\log K_X = \log [\text{ring}]/[\text{chain}]$, and σ^+ = the Hammett constant.[10] The sum of the

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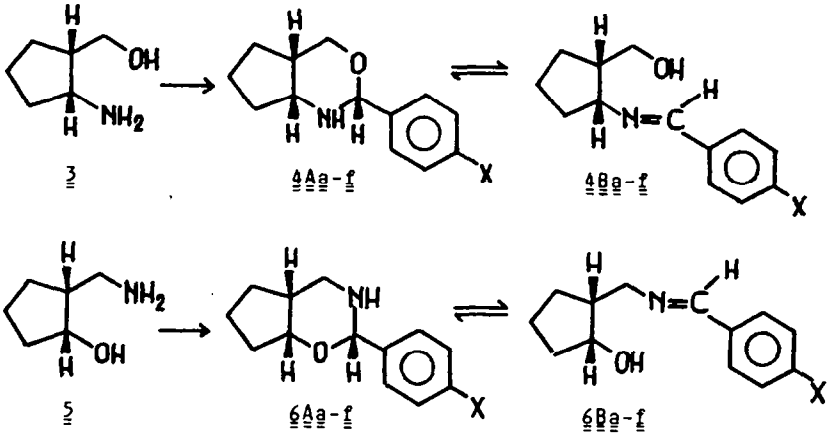
steric and electronic effects for the substituted oxazines was given as c = log K_X - log K_0, where log K_0 = -0.15 (log [ring]/[chain] for 2-phenyltetrahydro-1,3-oxazine). In other words, the constant c is the difference between the intercepts for the basic (1) and the substituted ring systems. A high value of c means a stabilization of the ring form, while a negative c value shows a destabilization effect due to the substitution of the ring form.[2]

Our present aim was a comparative investigation of the ring-chain tautomerism of 1,3-oxazines condensed with the cyclopentane ring.

RESULTS AND DISCUSSION

Through condensation of cis-2-hydroxymethylcyclopentylamine (3) or cis-2-aminomethylcyclopentanol (5) with aromatic aldehydes, six 2-aryl-substituted 1,3-oxazine derivatives (4a-f and 6a-f) were prepared in each case. The syntheses were performed in ethanol at room temperature. Since the open-chain form predominates in the trans series and the proportion of the ring form is fairly small, the relative experimental error is high. Therefore, only two representatives (8a,b and 10a,b) were prepared from each of the corresponding trans-1,3-aminoalcohols 7 and 9 (Scheme 2).

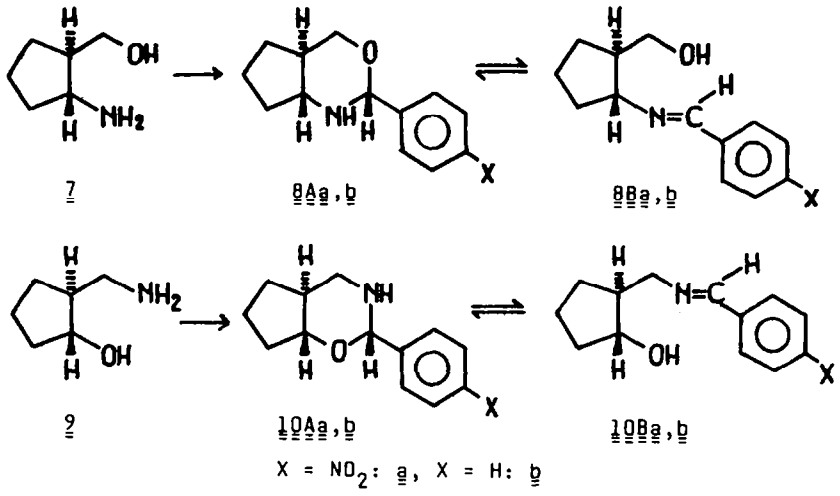


Scheme 1

The tautomeric ratios were based on the integrals of well-separated proton signals (Table 4). In the 400 MHz spectra, the signals of the C-2 methylene protons of the ring form and the corresponding methine protons of the open-chain form were usually the best choice. The characteristic data are given in Tables 2 and 3.

The ring-closures always proved to be stereospecific,[11,12] the NMR spectra indicating the presence of a single 1,3-oxazine derivative only, with the relative configuration shown in Schemes 1 and 2.

In parallel with the earlier findings[13] on the cyclohexane-condensed tetramethylene analogues, the vicinal coupling constants between the C-4 or C-6 methylene protons and H-5 of the hetero ring of the cis isomers indicate two theoretically possible main conformations, of which the O-inside or N-inside forms predominate, respectively.



X = NO_2: a, X = H: b

Scheme 2

When equation (1) was applied to the log K values for the cis isomers 4 and 6, satisfactory linear correlations were obtained against the Hammett σ^+ values[10] (Fig. 1, Table 1). The slopes of the plots correspond within experimental error to that in equation (1). The c values, the sums of the steric and electronic effects of the oxazine substituents,[2] are relatively small [4: 0.07 (0.95), 6: 0.31 (0.57); the c values of the corresponding perhydrobenzoxazine homologues are shown in parentheses],[2] which shows that the strain due to the cyclopentane ring fusion clearly destabilizes the oxazine ring.

Figure 1. The Hammett plots (equation 1) for compounds 4 (□) and 6 (○)

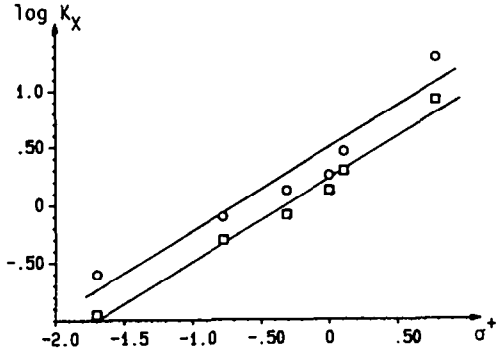


Table 1. Linear regression analysis data on compounds 4 and 6

Compound	4	6
No. of points	6	6
Slope	0.72	0.71
Intercept	0.22	0.46
Standard error in the slope	±0.05	±0.10
Standard error in the intercept	±0.04	±0.09
Correlation coefficient	0.991	0.960

For the trans counterparts 8 and 10, the destabilization effect is considerably higher. The 2-phenyl-substituted derivatives 8b and 10b contain merely 1.1 and 4.7% of the ring form, and accordingly the estimated c values are very low (~-3.1 and ~-1.5, respectively).

Although the free energy difference (2.9 kJ/mol)[16] between cis and trans-hydrindane is only slightly in favour of the trans isomer, the ring-closure reactions of cis and trans-1,2-disubstituted 1,3-difunctional cyclopentane derivatives leading to the 1,3-heteroanalogues of trans-hydrindane derivatives exhibited a very considerable difference.[16,17] For instance, some trans-1,2-disubstituted 1,3-difunctional cyclopentane derivatives, e.g. 2-hydroxy-1-carboxamides[18] or trans-2-hydroxymethylcyclopentanol,[19] could not be cyclized with aldehydes to the corresponding trans-fused 1,3-heterocyclanes. However, these

compounds underwent an easy ring-closure, when 1,3-heterocyclanes with a delocalized bond system were formed.[16,17] The above results on the ring-chain tautomerism of compounds 4, 6, 8 and 10 are in agreement with these literature data.

Table 2. Selected ^{1}H NMR chemical shifts (ppm) and coupling constants (Hz) for compounds 4a-f and 8a,b[a]

	Ring form							Chain form						
No.	H-2	H-4	H-6eq	H-6ax	$J_{6ax,6eq}$	$J_{6eq,5}$	$J_{6ax,5}$	H-2	H-4	H-6eq	H-6ax	$J_{6ax,6eq}$	$J_{6eq,5}$	$J_{6ax,5}$
4a	5.16	3.54	4.20	4.16	-12.0	0.9	2.3	8.38	4.02	3.63	3.75	-11.1	3.8	7.2
4b	5.05	3.50	4.16	4.12	-11.7	1.4	2.3	8.23	3.93	3.61	3.75	-11.3	3.8	7.3
4c	5.08	3.51	4.17	4.13	-11.9	1.5	2.3	8.26	3.95	3.62	3.77	-11.3	3.6	7.3
4d[b]	5.05	3.50	4.14	4.11	-12.0	1.5	[c]	8.21	3.92	3.62	3.77	-11.3	3.7	7.3
4e[b]	5.04	3.50	4.14	4.11	-13.0	1.3	2.4	8.19	3.92	3.62	3.78	-11.4	3.6	7.3
4f[b]	5.01	3.49	4.13	4.12	[c]	[c]	[c]	8.12	3.90	3.63	3.78	-11.3	3.4	7.5
8a	5.15	[c]	3.80	4.48	-10.7	[c]	4.1	8.36	3.48	3.61	3.65	-10.7	6.1	6.4
8b	5.08	[c]	3.80	4.43	-10.7	1.0	4.0	8.26	3.48	3.59	3.65	-10.5	6.4	6.4

[a] For easier comparability of the spectroscopic data on the ring and chain forms, the same numbering system has been used. [b] δCH_3 ring/chain, 4d: 2.32/2.36; 4e: 3.79/3.83; 4f: 2.92/3.01 ppm. [c] Cannot be determined because of the overlapping lines.

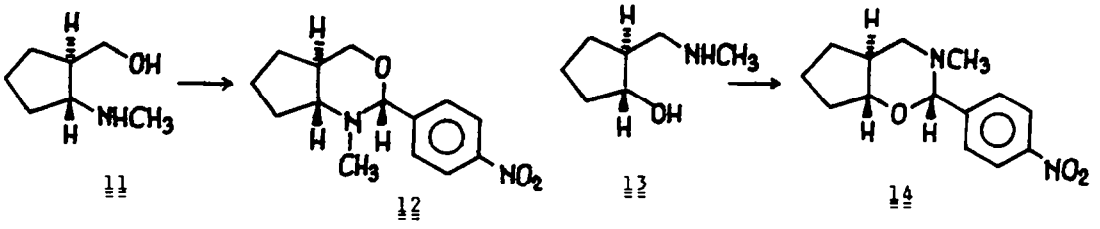
Table 3. Selected ^{1}H NMR chemical shifts (ppm) and coupling constans (Hz) for compounds 6a-f and 10a,b[a]

	Ring form							Chain form						
No.	H-2	H-4ax	H-4eq	H-6	$J_{4ax,4eq}$	$J_{4ax,5}$	$J_{4eq,5}$	H-2[b]	H-4ax	H-4eq	H-6	$J_{4ax,4eq}$	$J_{4ax,5}$	$J_{4eq,5}$
6a	5.14	3.43	3.16	4.24	-14.3	2.8	0	8.36	3.87	3.94	4.40	-12.3	7.2	5.5
6b	5.03	3.40	3.12	4.19	-14.2	3.13	0	8.19	3.76	3.90	4.38	-12.2	7.0	5.0
6c	5.07	3.41	3.12	4.20	-14.3	3.7	0	8.22	3.76	3.93	4.40	-12.1	6.7	5.0
6d[c]	5.02	3.38	3.09	4.19	-14.3	3.5	0	8.16	3.73	3.88	4.38	-12.1	6.7	4.9
6e[c]	5.02	3.40	3.12	4.19	-14.1	3.5	0	8.15	3.72	3.90	4.39	-12.1	6.7	4.9
6f[c]	5.01	3.40	3.19	4.19	-14.2	3.6	0	8.07	3.68	3.96	4.42	-12.1	6.3	4.3
10a	5.14	2.82	3.15	4.26	-13.4	11.3	0	8.38	3.73		4.10		7.2	
10b	5.07	2.84	3.16	4.20	-13.3	11.1	0	8.26	3.63	3.68	4.08	-11.9	9.0	5.8

[a] See Table 2, footnote a. [b] For all compounds, H-2 shows long-range couplings (from 0.5 to 1.6 Hz) with both of the H-4 protons. [c] δCH_3 ring/chain, 6d: 2.32/2.37; 6e: 3.77/3.82; 6f: 2.92/3.02 ppm.

Since the presence of the ring form was detected in products 8 and 10, the N-methyl-substituted ring forms 8A and 10A should be stable. The N-methylamino-alcohol 11 was prepared from 7 with ethyl chloroformate, followed by $LiAlH_4$ reduction, while compound 13 was obtained from the corresponding 2-hydroxycarboxamide by our earlier procedure.[16] The reaction of p-nitrobenzaldehyde with 11

or 13 resulted stereospecifically in compound 12 or 14, with relative configurations (r-4,c-2,t-5) and (r-6,c-2,t-5), respectively (Scheme 3).



Scheme 3

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a JEOL GX 400 MHz FT-NMR spectrometer in $CDCl_3$ solution, at ambient temperature, using TMS as internal standard. The number of scans was 40; if the proportion of one of the tautomeric forms was less than 5%, the number of scans was 80. In general, the ring-chain tautomeric ratios were based on the integrals of the respective methylene and methine proton signals at ~8.2 and ~5.1 ppm. If necessary, other well-separated signals were also used.

Melting points are uncorrected.

Reaction of aminoalcohols 3, 5, 7 and 9 with aromatic aldehydes

The aminoalcohol (3, 5, 7 or 9)[20] (0.23 g; 2 mmol) was dissolved in ethanol (15 ml) and a p-substituted benzaldehyde (2 mmol) was added. After standing for 3 h at room temperature, the solvent mixture was removed by evaporation and the products 4a, 4f, 6a and 6f were crystallized from hexane. The other products were oily. In the case of these derivatives the evaporation was repeated after the addition of 10 ml of benzene. After drying for 24 h in vacuum at room temperature, the oily products gave correct analytical data (Table 3).

trans-N-Methyl-2-hydroxymethylcyclopentylamine (11)

trans-2-Hydroxymethylcyclopentylamine[20] 3 (1.15 g; 0.01 mol) was dissolved in benzene (20 ml) and 10 ml of 8% aqueous NaOH and ethyl chloroformate (1.05 ml, 0.011 mol) were added with stirring. After 30 min the benzene layer was separated from the mixture and dried (Na_2SO_4), and the solvent was evaporated. The resulting colourless oil was added to a stirred suspension of $LiAlH_4$ (0.76 g; 0.02 mol) in dry THF (50 ml). The mixture was stirred and refluxed for 20 min, then cooled with ice, and water (2 ml) in THF (20 ml) was added dropwise. After stirring for 30 min, the inorganic material was filtered off. After drying (Na_2SO_4) of the filtrate and evaporation of the THF, the aminoalcohol 11 was obtained as a colourless oil (yield 67%). A small amount of the product was converted to the picrate for analysis. M.p. 119-121 °C (acetone/ether). (Found: C, 43.60; H, 5.18; N, 15.75. $C_{19}H_{18}N_4O_8$ requires: C, 43.58; H, 5.06; N, 15.64%).

(r-4,c-2,t-5)-N-Methyl-2-p-nitrophenyl-4,5-trimethylenetetrahydro-1,3-oxazine (12)

The aminoalcohol 11 (0.26 g; 2 mmol) was refluxed with p-nitrobenzaldehyde (0.30 g; 2 mmol) in ethanol (15 ml) for 12 h. The solvent was then evaporated off and the product was recrystallized from hexane, m.p. 128-129 °C, yield 52%. (Found: C, 64.21; H, 7.01; N, 10.47. $C_{14}H_{18}N_2O_3$ requires: C, 64.10; H, 6.92; N, 10.68%.)

Table 4. Physical and analytical data on the compounds prepared (4, 6, 8, 10)

Compound	M.p. (°C)	% of the ring form	Found % C	H	N	Formula (M.W.)	Requires % C	H	N
4a	85-87[a,b]	97	62.65	6.61	11.10	$C_{13}H_{16}N_2O_3$ (248.28)	62.88	6.50	11.29
4b	c	74	65.83	6.94	5.92	$C_{13}H_{16}ClNO$ (237.73)	65.68	6.79	5.89
4c	c	64	76.48	8.61	6.84	$C_{13}H_{17}NO$ (203.28)	76.81	8.43	6.89
4d	c	57	77.20	8.97	6.50	$C_{14}H_{19}NO$ (217.30)	77.38	8.81	6.45
4e	c	44	72.41	8.38	6.13	$C_{14}H_{19}NO_2$ (233.30)	72.07	8.21	6.00
4f	65-67[a]	21	73.23	9.33	11.37	$C_{15}H_{22}N_2O$ (246.35)	73.13	9.00	11.37
6a	80-81[a,d]	89	62.88	6.67	11.47	$C_{13}H_{16}N_2O_3$ (248.28)	62.88	6.50	11.29
6b	c	66	65.68	6.91	6.02	$C_{13}H_{16}ClNO$ (237.73)	65.68	6.79	5.89
6c	c	57	76.76	8.39	6.81	$C_{13}H_{17}NO$ (203.28)	76.81	8.43	6.89
6d	c	45	77.20	9.13	6.50	$C_{14}H_{19}NO$ (217.30)	77.38	8.81	6.45
6e	c	33	72.14	8.39	6.13	$C_{14}H_{19}NO_2$ (233.30)	72.07	8.21	6.00
6f	103-104[a]	9	73.19	9.14	10.49	$C_{15}H_{22}N_2O$ (246.35)	73.13	9.00	10.37
8a	c	1.3	62.84	6.66	11.19	$C_{13}H_{16}N_2O_3$ (248.28)	62.88	6.50	11.29
8b	c	1.1	76.93	8.70	6.97	$C_{13}H_{17}NO$ (203.28)	76.81	8.43	6.89
10a	c	7.3	62.76	6.71	11.14	$C_{13}H_{16}N_2O_3$ (248.28)	62.88	6.50	11.29
10b	c	4.7	76.71	8.39	6.78	$C_{13}H_{17}NO$ (203.28)	76.81	8.43	6.89

[a] From n-hexane. [b] Lit.[21] m.p. 84.5-85.5 °C. [c] Almost colourless or light-yellow viscous oil. [d] Lit.[21] m.p. 80-81 °C.

^{1}H NMR δ = 8.22, 7.66 (dd, 4H, aromatic protons), 4.37 (s, 1H, H-2), 4.30 (q, 1H, H-6eq, J = 4.3, -10.5 Hz), 3.48 (t, 1H, H-6ax, J = 10.5, -10.5 Hz), 1.92 (s, 3H, N-CH_3), 1.2-2.1 ppm (m's, 8H, aliphatic protons).

(r-6,c-2,t-5)-N-Methyl-2-p-nitrophenyl-5,6-trimethylenetetrahydro-1,3-oxazine (14)

Oxazine 14 was prepared similarly as 12, but starting from the aminoalcohol 13.[16] M.p. 87-89 °C, yield 61%. (Found: C, 64.08; H, 7.14; N, 10.67. $C_{14}H_{18}N_2O_3$ requires: C, 64.10; H, 6.92; N, 10.68%.)

^{1}H NMR δ = 8.22, 7.67 (dd, 4H, aromatic protons), 4.92 (s, 1H, H-2), 3.33 (m, 1H, H-6, J = 11.8 Hz), 3.29 (m, 1H, H-4eq, J = -11.8, 6.3 Hz), 2.63 (t, 1H, H-4ax, J = -11.8, 11.8 Hz), 2.04 (s, 3H, N-CH_3), 1.1-2.0 ppm (m's, 7H, aliphatic protons).

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