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STEREOCHEMICAL STUDIES—54[1]. SATURATED HETEROCYCLES—35[1]

SYNTHESIS AND CONFORMATIONAL ANALYSIS OF STEREOISOMERIC 2-OXO- AND 2-THIOXO-*CIS*- AND *TRANS*-5,6-TRIMETHYLENE-3,4,5,6-TETRAHYDRO-1,3-OXAZINES

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Abstract—*cis*- and *trans*-5,6-Trimethylene-3,4,5,6-tetrahydro-1,3-oxazin-2-ones ane 2-thiones (**11–20**) were synthesized from *cis*- and *trans*-2-*aminomethylcyclopentanols* (**6–10**) by reaction with urea, ethyl chloroformate, carbon disulphide, or thiophosgene. The cyclization reactions were also successful with the *trans*-amino-alcohols, at variance with earlier literature data relating to 1,2-disubstituted 1,3-bifunctional *trans*-cyclopentane derivatives. X-Ray diffraction analysis of *trans*-5,6-trimethylene-3,4,5,6-tetrahydro-1,3-oxazine-2-thione (**17**) shows that the exocyclic C—S sp^2 bond takes part in a co-planar delocalized $p\pi$–$p\pi$ bond system formed on the S(10), O(1), N(3) and C(2) atoms, and consequently both the C(2)–N(3) [1.304(7) Å] and C(2)–O(1) [1.337(7) Å] bonds gain some multiple bond character. The endocyclic bond angles at C(2) and N(3) are significantly opened, compared with those in related heterocycles. Of the bonds in the six-membered hetero ring, C(5)–C(6) is significantly shortened [1.448(9)Å]. The remarkable ring-closure reaction of the *trans* cyclopentane derivatives can be explained by the above findings. ^{1}H NMR data on compounds **11–20** suggest conformationally homogeneous systems and the predominance of the *O*-inside conformers of the *cis* isomers.

In previous communications we reported the synthesis of fused-skeleton dihydro-[2] and tetrahydro-1,3-oxazines[3,4] and oxazin-2-ones[5,6] from *cis*- and *trans*-2-aminomethylcyclohexanol, *cis*- and *trans*-2-hydroxymethylcyclohexylamine and the homologous cycloheptane derivatives, and we made a kinetic study of the N → O acyl migration[7–9] of the starting 1,3-aminoalcohols. Though the *trans* 1,3-aminoalcohols having a cyclohexane, cycloheptane or cyclooctane skeleton show higher reactivity than the corresponding *cis* isomers in this reaction, the rates of the acyl migration reactions occurring through a bicyclic transition state do not differ in order of magnitude (k_{trans}/k_{cis} = 2–4). No appreciable difference in the reactivity of the *cis* and *trans* isomers was found either in the ring-closure reactions of 1,2-disubstituted 1,3-bifunctional cyclohexane and cycloheptane derivatives, such as the cyclizations of 2-hydroxy-1-carboxamides or 2-amino-1-carboxylic acid derivatives, leading to tetramethylene- and pentamethylene-1,3-oxazin-4-one,[10,11] -1,3-oxazin-2-one,[12] -1,3-oxazine-2-thione[12] or pyrimidin-4-one.[13]

In contrast, a very significant difference in reactivity was observed when the *cis* and *trans* isomers of 2-aminomethylcyclopentanol (**6** and **7**, respectively) were cyclized. Ring-closure of the *cis* compound was readily effected with aldehydes to afford *cis*-5,6-trimethylene-1,3-oxazine,[3,4] but the *trans* isomer (**7**) failed to react under identical conditions.[4]

The rates of the N→O acyl migrations of the cyclopentane derivatives **6** and **7**, occurring through the tetrahydro-1,3-oxazine transition state, also showed a difference amounting to several orders of magnitude, in favour of the *cis* isomer. This is explained by the rapid N → O acyl migration in *N*-benzoyl-*cis*-2-aminomethylcyclopentanol occurring with retention, whereas in the *trans* isomer the widely separated functional groups require inversion of the configuration for the occurrence of the reaction, and the product is the *cis*-O-benzoyl derivative.[14,15]

Surprisingly, there are only very few examples in the literature concerning the highly different reactivities of *cis*- and *trans*-1,2-disubstituted 1,3-cyclopentane derivatives. Finch *et al.*[16] described the separation of the *cis*- and *trans*-2-hydroxymethylcyclopentanol isomers by virtue of the fact that the *trans* compound did not undergo ring-closure to *trans*-trimethylene-1,3-dioxane. Analogous findings in our laboratory were that *trans*-2-aminocyclopentanecarboxylic acid or *trans*-2-hydroxycyclopentanecarboxamide could not be cyclized with imidates, aldehydes or ketones to *trans*-5,6-trimethylenepyrimidin-4-one[13] and -1,3-oxazin-4-one,[10] respectively.

In the present paper we report successful ring-closure reactions of *cis*- and *trans*-2-aminomethylcyclopentanols (**6**, **7**) and their *N*-substituted derivatives (**8–10**). X-Ray diffraction analysis of *trans*-5,6-trimethylene-3,4,5,6-tetrahydro-1,3-oxazine-2-thione (**17**) has led to an explanation of the very interesting ring-closure of these *trans*-1,2-disubstituted 1,3-bifunctional derivatives.

Carboxamides **1**, **2**[15] and **3**, **4** were prepared from the appropriate *cis* and *trans* ethyl 2-hydroxy-1-cyclopentane-

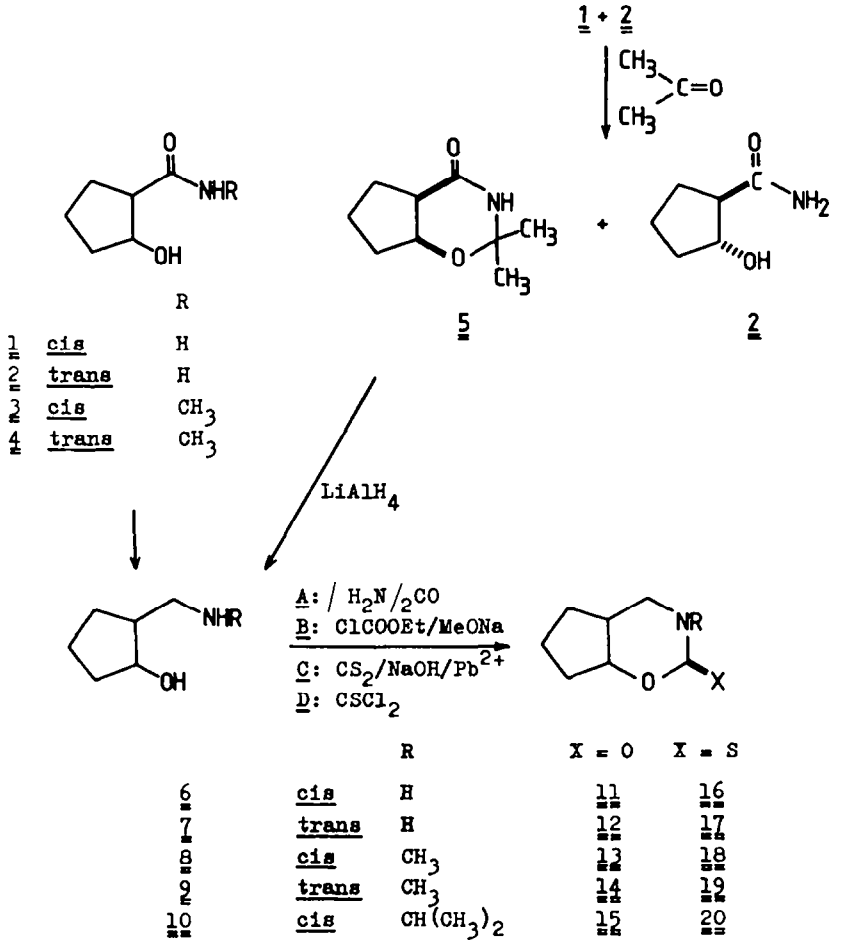
carboxylates[17] (Scheme 1). Lithium aluminium hydride reduction of compounds **1–4** gave the corresponding aminoalcohols **6**, **7**[15] and **8**, **9**.

The *N*-isopropyl derivative **10** was synthesized from 2-hydroxy-1-carboxamide **1** readily converted by aldehydes and ketones into 1,3-oxazin-4-ones,[10,11] which are reduced by lithium aluminium hydride to 1,3-aminoalcohols. Of the 2-hydroxycyclopentanecarboxamides **1** and **2** only the *cis* isomer undergoes cyclization, and hence the reaction of a *cis*-*trans* mixture, involving the formation of stereohomogeneous *cis*-5,6-trimethylene-1,3-oxazin-4-ones, gives finally *N*-substituted *cis*-2-aminomethylcyclopentanols.[18]

The above-mentioned property of the *trans*-1,2-disubstituted 1,3-bifunctional cyclopentane derivatives, namely their failure to form *trans*-trimethylene-bridged, saturated, six-membered 1,3-hetero rings, is particularly remarkable if the analogous carbocycles, the hydrindanes, are considered. *trans*-Hydrindane has a rigid conformation, yet the energy difference between *cis*- and *trans*-hydrindane is very small (2.9 kJ mol^{-1}). For comparison, the energy content of *cis*-decalin is about 10 kJ mol^{-1} higher than that of *trans*-decalin. The smaller energy difference between the hydrindane isomers is due to the less puckered character of the five-membered ring.

The lower energy content of *trans*-decalin than that of *cis*-decalin is consistent with the relative reactivities of the *cis*- and *trans*-2-disubstituted 1,3-bifunctional cyclohexane derivatives, when the resulting compounds are decalin-like heterocycles containing 1,3-hetero-atoms,[2] or the bicyclic transition state of the reaction is a heterocycle related to decalin (e.g. in the case of the N→O acyl migration[7,8] of 2-aminomethylcyclohexanol and 2-hydroxymethylcyclohexylamine). The very small energy difference between *cis*- and *trans*-hydrindane, however, does not explain the highly different reactivities of the *cis*- and *trans*-1,2-disubstituted 1,3-bifunctional cyclopentane derivatives if the expected reaction product,[10,13] or the transition state,[14] is a hydrindane derivative containing two hetero atoms in the six-membered ring.

We presumed that in our synthetic targets, the *cis*- and *trans*-5,6-trimethylene-1,3-oxazin-2-ones (**11–15**) and -2-thiones (**16–20**), the six-membered ring would become more flattened owing to conjugation occurring between the oxygen or sulphur atom attached to the sp^2 C-2 atom, and the neighbouring hetero atom. Thereby the whole bicyclic molecule would be less puckered, and hence the energy difference between the *cis* and *trans* isomers lowered, and so the synthesis of the *trans*



Scheme 1.

Table 1. Physical and analytical data on the compounds prepared (3, 4, 8–20)

Compound no.	Method	M.p. °C	Recryst.[c]	Yield %	Found % C	Found % H	Found % N	Formula	Required % C	Required % H	Required % N
3		77–79	Bz-n-Hexane	89	58.95	9.30		$C_7H_{13}NO_2$	58.72	9.15	
4		76–77	Bz	84	59.10	9.38		$C_7H_{13}NO_2$	58.72	9.15	
8		56–58	n-Hexane	49	64.92	11.81		$C_7H_{15}NO$	65.08	11.70	
9[a]		150–153	EtOH	55	43.52	5.13	15.30	$C_{13}H_{18}N_4O_8$	43.58	5.06	15.64
10[b]		128–130	EtOH-Et_2O	78	56.10	10.70		$C_9H_{20}ClNO$	55.80	10.41	
11	A	91–93	EtOH	24	59.75	8.00	10.08	$C_7H_{11}NO_2$	59.56	7.85	9.92
12	B	149–151	Bz-Pe	26	59.25	7.97	9.65	$C_7H_{11}NO_2$	59.56	7.85	9.92
13	B	44–45	EtOAc-Pe	23	61.65	8.21	9.00	$C_8H_{13}NO_2$	61.91	8.44	9.03
14	B	83–85	EtOAc-Pe	24	61.69	8.30	8.92	$C_8H_{13}NO_2$	61.91	8.44	9.03
15	B	59–61	EtOAc-Pe	20	65.37	9.25	7.71	$C_{10}H_{17}NO_2$	65.54	9.35	7.64
16	C	122–124	EtOH	42	53.50	7.30	8.71	$C_7H_{11}NOS$	53.47	7.05	8.91
17	C	196–198	EtOH	27	53.49	6.92	9.10	$C_7H_{11}NOS$	53.47	7.05	8.91
18	D	42–44	EtOAc	23	52.60	8.35	8.94	$C_7H_{13}NOS$	52.80	8.23	8.80
19	D	142–144	Bz-Pe	30	56.38	7.87	8.27	$C_8H_{13}NOS$	56.11	7.65	8.18
20	D	96–98	Bz-Pe	21	60.12	8.64	6.91	$C_{10}H_{17}NOS$	60.26	8.60	7.03

[a] Picrate

[b] Hydrochloride; found Cl 18.22, calcd. Cl 18.30%.

[c] Bz = benzene; Pe = petroleum ether

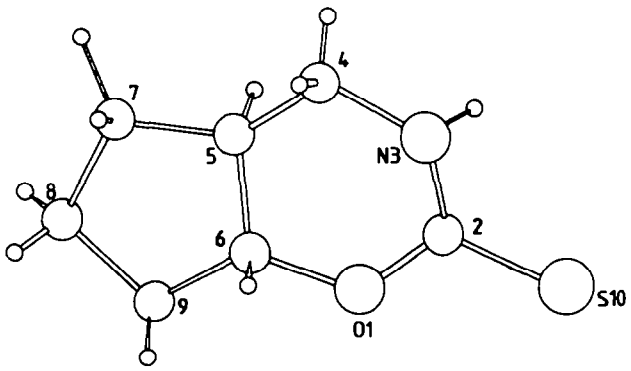


Fig. 1. A perspective view of the molecule 17 with atomic numbering. Atoms are carbon unless indicated otherwise. The numbering of H atoms in Table 3, follows that of the corresponding non-hydrogen atoms.

Table 2. Atomic coordinates ($\times 10^4$). Esd's are given in parentheses

Atom	x/a	y/b	z/c	B_{eq}
S(10)	3716(2)	752(2)	3423(1)	4.32(6)
O(1)	606(6)	2143(4)	4092(3)	4.14(16)
C(2)	2176(8)	1360(5)	4434(5)	3.31(21)
N(3)	2418(7)	1101(4)	5503(4)	3.59(19)
C(4)	1247(9)	1633(6)	6461(5)	3.69(22)
C(5)	-8(10)	2752(7)	6033(5)	5.01(28)
C(6)	-997(10)	2430(7)	4956(5)	5.25(29)
C(7)	-1891(10)	3265(7)	6665(5)	5.00(28)
C(8)	-3171(9)	4000(7)	5760(5)	4.78(28)
C(9)	-2360(9)	3565(6)	4622(5)	4.34(25)

B_{eq} = 4/3*TRACE (B*G)

Table 3. Atomic coordinates ($\times 10^3$) for hydrogen atoms. Esd's are given in parentheses

Atom	x/a	y/b	z/c	B_{iso}
H(3)	316(8)	59(5)	567(4)	4.0(10)
H(4A)	43(8)	94(5)	681(4)	4.4(10)
H(4B)	208(8)	185(5)	707(4)	4.2(10)
H(5)	116(10)	352(7)	593(6)	10.0(10)
H(6)	-181(10)	153(7)	517(6)	8.3(10)
H(7A)	-274(9)	260(6)	704(5)	5.7(10)
H(7B)	-145(9)	376(6)	734(5)	5.8(10)
H(8A)	-289(9)	498(6)	586(5)	5.7(10)
H(8B)	-449(10)	384(6)	584(5)	6.8(10)
H(9A)	-160(9)	422(6)	418(5)	5.6(10)
H(9B)	-304(9)	333(6)	414(5)	5.8(10)

isomers would be possible. This expectation has been fully substantiated experimentally.

The 5,6-trimethylene-3,4,5,6-tetrahydro-1,3-oxazin-2-ones were synthesized from the starting aminoalcohols by fusion with urea[6,20] (**11**) (Method A), or by cyclization with sodium methoxide of the ethyl carbamates prepared by means of ethyl chloroformate[21] (**12–15**) (Method B). The oxazine-2-thiones **16** and **17** were made by ring-closure of the dithiocarbamates[22] obtained from the aminoalcohols **6** and **7** (Method C), or by treatment of the aminoalcohols **8–10** with thiophosgene (Method D), affording the *N*-substituted derivatives **18–20** (Table 1).

X-Ray determination of the molecular structure of the trans-*trimethylene derivative* **17**

Figure 1 shows a perspective view of the structure computed from the final fractional atomic coordinates given with their esd values in Tables 2 and 3. The bond lengths and angles (Fig. 2) agree in general with the corresponding literature values. The exocyclic S⋯C (sp^2) distance [1.678(5) Å] resembles those in 1-phenylthiosemicarbazide [1.696(2) Å][23] and 4-phenylthiosemicarbazide [1.685(5) Å][24]. This S⋯C bond takes part in a co-planar delocalized $p\pi$–$p\pi$ bond system formed on the S(10), O(1), N(3) and C(2) atoms; consequently, both C(2)–N(3) [1.304(7) Å] and C(2)–O(1) [1.337(7) Å] gain some multiple bond character. In accord with the V.S.E.P.R. theorem,[25] the endocyclic bond angles at C(2) and N(3) are significantly closed and opened [119.7(8) and 128.4(8) Å], respectively, as compared to those observed in 2-(*p*-chlorophenyl)-*cis*-5,6-tetramethylene-5,6-dihydro-4H-1,3-oxazine [126.7 and 119.6°] and 2-(*p*-chlorophenyl)-*cis*-4,5-tetramethylene-4,5-dihydro-6*H*-1,3-oxazine [126.6 and 119.3°].[7] Of the four single bonds in the six-membered hetero ring, C(5)–C(6) is distinguished by its significant shortening [1.448(9) Å].

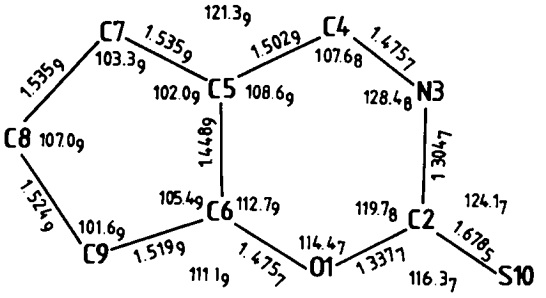


Fig. 2.

To shed light on this anomaly, the positions of C(5) and C(6) were carefully checked in difference electron density synthesis, which showed only two, somewhat smeared maxima. No positional disorder of these atoms could be established, however. In the final least squares procedure the positions of these two atoms were initially separated by 1.54 Å, but they were invariably shifted back to the original centres of electron density observed in the difference Fourier map. Accordingly, this bond shortening may be correlated with the difficulty observed in the ring-closure reactions of the *trans*-1,2-disubstituted 1,3-bifunctional compounds discussed above.

The conformation of the molecule is given by the torsion angles (Table 4). As shown by the lowest asymmetry factors,[26] fC_2(C2–C3) = 0.8 pm for the hetero ring and fC_2(C8) = 2.0 pm for the carbocyclic ring, the puckering of the *trans*-fused rings creates a two-fold axis which bisects the C(2)–N(3) and C(5)–C(6) bonds and the C(8) atom. The puckering parameters[27] $Q = 0.48$ Å, $\varphi = 268.6°$, $\theta = 53.1°$ for the six-membered ring and $Q = 0.43$ Å, $\varphi = 345.4°$ for the cyclopentane ring, indicate half-chair conformations of both rings. The molecules form dimers bound by centre of symmetry related N(3)–H(3)⋯S(10) hydrogen-bond pairs [N⋯S = 3.33(5), H⋯S = 2.62(5) Å, NH⋯S = 165(5)°]. (According to Pauling,[28] the van der Waals radius for S is 1.85 Å.)

C(4)-N(3)-C(2)-S(10)	176.1(11)
C(4)-N(3)-C(2)-O(1)	-4.7(9)
C(4)-C(5)-C(6)-O(1)	-62.6(8)
C(5)-C(4)-N(3)-C(2)	-11.7(8)
C(5)-C(6)-O(1)-C(2)	47.0(9)
C(6)-O(1)-C(2)-S(10)	167.0(8)
C(6)-O(1)-C(2)-N(3)	-12.3(8)
C(6)-C(5)-C(4)-N(3)	42.8(8)
C(7)-C(5)-C(4)-N(3)	160.3(12)
C(7)-C(5)-C(6)-O(1)	168.2(10)
C(7)-C(8)-C(9)-C(6)	10.8(8)
C(8)-C(7)-C(5)-C(4)	-158.8(10)
C(8)-C(7)-C(5)-C(6)	-38.1(8)
C(8)-C(9)-C(6)-O(1)	-158.0(9)
C(8)-C(9)-C(6)-C(5)	-35.6(8)
C(9)-C(6)-O(1)-C(2)	165.1(11)
C(9)-C(6)-C(5)-C(4)	176.0(10)
C(9)-C(6)-C(5)-C(7)	46.8(8)
C(9)-C(8)-C(7)-C(5)	16.2(8)

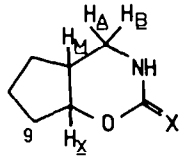
Conformational analysis by NMR *spectroscopy*

^{1}H NMR data on compounds **11–20** (Table 5) suggest conformationally homogeneous systems and, similarly to the related polymethylene perhydrooxazinones investigated earlier,[5,6,10,11] the predominance of the *O*-inside conformers (Scheme 2) for the *cis* isomers, of the two possible chair–half-chair conformations (*O*-inside and *O*-outside).

The principles and mode of the conformational analysis were described in detail[5] earlier, and hence only the most essential points will be treated briefly here. The deciding spectral parameters concerning the conformations are the coupling constant J_{AM}, the chemical shift δH_X and the half-bandwidth of the H_X signal.

The hydrogens *A* and *M* are in the *diaxial* position (with respect to the hetero ring) in the *trans* isomers and in the *O*-outside conformation of their *cis* pairs. In the *O*-inside comformers, however, these protons are in *equatorial* and *axial* positions, respectively. Consequently, a considerably smaller J_{AM} coupling constant is expected for the latter than for the former, due to the Karplus relation. Since a significant difference in the J_{AM}

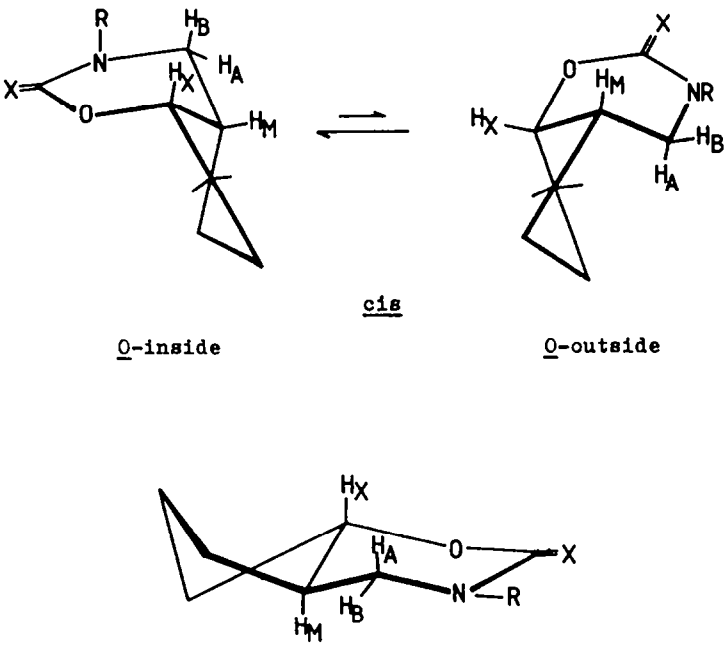
Table 5. ^{1}H NMR data in $CDCl_3$ ($\delta_{TMS} = 0$ ppm)*



Compound	δH_A [a]	δH_B [a]	J_{AB} [b]	J_{AM} [b]	J_{BM} [b]	δH_X m (1H)	$\Delta\nu H_X$ [c]	δ(3xCH_2 + H_M) [d]	δR [e]
11*	3.26	3.61	12	4	4	4.75	7	~1.9	~6.95 s(1H)
12*	3.10	3.50	10	10	5	4.10	25	~1.9	~6.6 s(1H)
13	3.14	3.61	12.1	5.6	2.5	4.68	10	1.4-2.5	2.97 s(3H)
14	3.20	3.35	10.8	10.8	5.6	4.02 [h]	-	1.2-2.2	2.99 s(3H)
15	3.05	3.38	12.2	5.2	3.5	4.65	12	1.5-2.4	1.12 [f], 1.15 [f], 4.56 [g]
16*	3.27	3.58	14	4	2	4.75	6	~1.9	~9.0 s(1H)
17*	3.16	3.56	12	12	6	~4.1	24	~1.9	~8.95 s(1H)
18	3.28	3.68	13.2	5.8	3.0	4.68	12	1.5-2.5	3.43 s(3H)
19	3.38	3.57	12.0	12.0	5.4	3.98 [h]	-	1.2-2.2	3.41 s(3H)
20	3.06	3.43	13.0	5.6	5.1	4.66	15	1.4-2.6	1.20 [f], 1.23 [f], 5.48 [g]

* at 60 (11,12,16,17) or 250 MHz (13-15, 18-20). IR data (in KBr), cm^{-1}: νC=X, νC-O: 11 1680; 12 1660, 1110; 13 1645, 1235; 14 1665, 1235; 15 1660, 1210; 16 1175 1145 1050; 17 1175 1157 1090; 18 1270 1235, 1154-1145 1130; 19 1250 1230, 1175; 20 1190, 1135.

[a] From the AB part of the ABMX multiplet.
[b] Coupling constants in Hz, J_{AM} and J_{BM} are given by AMX approximation.
[c] Half-bandwidth of the X signal in Hz.
[d] Overlapped multiplet of 7H intensity.
[e] Broad signal if R = H.
[f] d, J = 6.6 Hz(3H).
[g] sp (1H).
[h] 2xt, J = 10, 10 and 8 Hz.



Scheme 2.

values was observed in all cases of *cis-trans* pairs (4–6 Hz for the former, and 10–12 Hz for the latter), the *O*-inside form can be regarded as the proved predominant conformation of the *cis* isomers.

For cyclohexanes and their hetero analogues the relation $\delta H_e > \delta H_a$ is generally characteristic, due to the anisotropy of the carbon–carbon bonds in the ring, which shield the *axial* hydrogens. In respect of the cyclopentane ring, the *X* proton is *quasiequatorial* in the *O*-inside, and quasiaxial in the *O*-outside conformers; consequently, greater chemical shifts are to be expected for the former than for the latter, which at the same time have δH_X values similar to those of their *trans* pairs which contain an *axial X* atom, too. The *O*-inside form of the *cis* isomers is supported by the considerable difference between the δX shifts of the isomer pairs.

Finally, there is a difference in the half-bandwidth of the H_X signal ($\Delta\nu H_X$) in the case of *cis-trans* pairs. The $^3J^{cis}$ and $^3J^{trans}$ couplings in cyclopentanes are similar in magnitude due to the flexibility (fast pseudorotation) of the five-membered ring. There is no difference between the conformers as concerns the J_{MX} values. It is an *axial-equatorial* interaction in both cases, and consequently the difference in the $\Delta\nu H_X$ values of the *cis-trans* pairs points to a partly rigid structure of the five-membered ring, with the dihedral angles between the C – H_X and the two neighbouring (C_γ–H) methylene bonds (H-9 *cis* and H-9 *trans*) similar to those of a *cis*-decalin ring system (~60° and ~180°).

EXPERIMENTAL

^{1}H NMR spectra were recorded at 60 and 250 MHz in $CDCl_3$ solution with JEOL 60 HL and Bruker WM-250-FT spectrometers at room temp, using TMS as internal standard.

Compounds **1**, **2** and **5**–**7** were prepared as described earlier.[15,17]

The physical properties, analyses and yields of the compounds are listed in Table 1.

N-*Methyl*-cis-2-*hydroxycyclopentanecarboxamide* **3**

Ethyl *cis*-2-hydroxycyclopentanecarboxylate[17] (4.74 g; 0.03 mol) was allowed to stand for 4 days at room temp in EtOH (50 ml) containing 20% methylamine. Evaporation to dryness gave white crystals. Compound **4** was made similarly from the *trans* ester.

cis-2-*Methylaminomethylcyclopentanol* **8**

$LiAlH_4$ (1.14 g; 0.03 mol) was suspended in dry tetrahydrofuran (100 ml) and *N*-methyl-*cis*-2-hydroxycyclopentanecarboxamide (**3**) (2.86 g; 0.02 mol) was added to the suspension in portions, during 10 min. The mixture was stirred and refluxed for 6 h, then decomposed by adding water (2.5 ml) under cooling in ice, and the inorganic material was removed by filtration. Evaporation of the filtrate left a pale yellow viscous oil, which was distilled on a Hickman still, b.p. 115–120° at 400 Pa. The distillate soon crystallized on standing. A sample for analysis was recrystallized from *n*-hexane.

trans-2-*M-ethylaminomethylcyclopentanol* **9**

This compound was prepared analogously to **8**, starting from *N*-methyl-*trans*-2-hydroxycyclopentanecarboxamide **4**. The amino alcohol **9** obtained on distillation was a colourless viscous oil, b.p. 133–137° at 400 Pa. A small amount of the product was converted to the picrate for analysis.

cis-2-*Isopropylaminomethylcyclopentanol* **10**

Prepared as amino-alcohol **8** from 2,2-dimethyl-5,6-trimethylene-3,4,5,6-tetrahydro-1,3-oxazin-4-one[29] (**5**) during 4 h. The product **10** obtained after distillation was a colourless, viscous oil, b.p. 146–152° at 400 Pa. A sample for analysis was prepared for analysis.

cis - 5,6 - *Trimethylene* - 3,4,5,6 - *tetrahydro* - 1,3 - *oxazin* - 2 - *one* **11**

Method A). *cis*-2-Aminomethylcyclopentanol (**6**) (1.7 g; 0.015 mol) and urea (8.4 g; 0.14 mol) were added to EtOH (200 ml)

saturated with HCl, and the mixture was evaporated to dryness in vacuo. The residue was heated on an oil-bath at 170° for 30 min, and then at 200° for 1 h. After cooling, the product was pulverized and extracted with hot $CHCl_3$ (3 × 50 ml). The combined extract was filtered and the solvent evaporated. The remaining thick oil was purified on a neutral alumina (Brockmann Grade II; 50 g) column by elution, first with petroleum ether–benzene–chloroform (10 : 5 : 3), and then with $CHCl_3$. The $CHCl_3$ fraction was evaporated to dryness; crystallization of the residue gave 0.95 g of **11**.

5,6 - *Trimethylene* - 3,4,5,6 - *tetrahydro* - 1,3 - *oxazin* - 2 - *ones* **12–15**

(*Method B*[21]). The amino-alcohol **7–10** (0.01 mol) was mixed with a solution of $NaHCO_3$ (0.84 g; 0.01 mol) in water (10 ml), ethyl chloroformate (0.55 g; 0.01 mol) was added, and the mixture was stirred and refluxed for 1 h. After cooling, it was extracted with Et_2O and dried (Na_2SO_4), and the solvent was evaporated. The residue was heated with sodium methoxide (50 mg) for 20 min on an oil-bath at 120°. The melt was extracted with hot EtOAc, and the residue of evaporation was recrystallized.

5,6 - *Trimethylene* - 3,4,5,6 - *tetrahydro* - 1,3 - *oxazine* - 2 - *thiones* **16** *and* **17**

(*Method C*[22]). The amino-alcohol **6**, **7** (1.9 g; 0.0165 mol) was cooled in an aqueous solution (10 ml) of KOH (1.1 g) to 0°, mixed with a solution of CS_2 (1.3 g) in dioxane (8 ml), and vigorously stirred for 5 min. KOH (0.55 g) in water (10 ml) and then lead(II) nitrate (5.5 g) dissolved in water (30 ml) were added, and the mixture was warmed to 60° during 10 min, with stirring. The hot solution was filtered from PbS, the latter was washed with hot water, and the combined aqueous solution was evaporated to dryness. Extraction with EtOH and evaporation gave a residue which was recrystallized.

5,6 - *Trimethylene* - 3,4,5,6 - *tetrahydro* - 1,3 - *oxazine* - 2 - *thiones* **18–20**

(*Method D*). Thiophosgene (1.15 g; 0.01 mol) dissolved in benzene was added dropwise, with cooling and stirring, to a solution of the amino-alcohol **8–10** (0.01 mol) and triethylamine (2 g; 0.02 mol) in dry benzene (10 ml). The mixture was stirred at room temp for 10 min, and then washed with water (3 × 15 ml). The organic phase was dried (Na_2SO_4), the solvent was evaporated, and the resulting red oil was dissolved in benzene, poured onto a column of silica gel, and eluted with benzene and then with EtOAc. The latter eluate was concentrated and the residue was recrystallized from benzene–petroleum ether.

Crystal structure determination of trans-5,6-*trimethylene*-3,4,5,6, *tetrahydro*-1,3-*oxazine*-2-*thione* **(17)**

Crystal data: $C_5H_{11}NOS$, MW = 157.24 monoclinic, a = 6.195(2) b = 10.613(2) c = 11.876(2) β = 91.22(2) U = 780.6 Å^3, D_c = 1.337 g · cm^{-3}, Z = 4, F(000) = 336, space group $P2_1/c$ (from systematic absences). Intensities of 1074 independent reflections were collected in the range $2\theta \leqq 50°$ by an ω–2θ scan on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated MoK_α (λ = 0.71073 Å) radiation. Cell constants were determined by least squares refinement from the setting angles of 25 reflexions. After data reduction, 1053 reflections with $I-2\sigma(I) > 0$ were taken as observed. No absorption (μ = 3.37 cm^{-1}) correction was applied. The structure was solved by a new version of MULTAN.[30] An E-map (ABSFOM 1.29 RESID 14.8), computed with the use of the phase set of 140 normalized structure factors having $E \geqq 1.64$, revealed the positions of all non-hydrogen atoms (R = 0.24). Full-matrix least-squares refinement of the positional and vibrational parameters reduced R to 0.087. At this stage H positions were generated from assumed geometries and checked by a subsequent difference map calculation. Further anisotropic refinement of heavy atom positions in which H positions were treated isotropically gave a final R = 0.068 (R_w = 0.07, R_{hH} = 0.079). As mentioned above, the features of the maxima belonging to the C(5) and C(6) atoms were checked in difference Fourier synthesis. Scattering factors were taken from *International Tables for X-Ray Crystallography*.[31] All calculations were performed on a PDP 11/34 minicomputer with the use of the SDP-34 system of Enraf-Nonius with local modifications.

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