Stereochemical Studies. Part 78. Saturated Heterocycles. Part 65.[1] Synthesis and Spectroscopic Studies of *cis*-5,6-Trimethylene-, and *cis*- and *trans*-5,6-Tetra- and -Pentamethylene-1,3-oxazinan-4-ones

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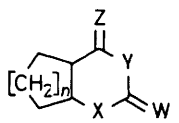
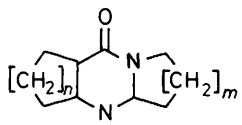
N-Methyl-*cis*-5,6-trimethylene-, and *cis*- and *trans*-5,6-tetra- and -pentamethylene-1,3-oxazinan-4-one derivatives (**15**) and (**16**) were prepared by cyclisation, with aldehydes, of the appropriate alicyclic 2-hydroxy-1-carboxamides. In each case, formation of the new C-2 centre of chirality was found to take place stereospecifically and only the (*r*-5,*t*-2,*t*-6) and (*r*-5,*c*-2,*c*-6) diastereoisomers, respectively, were formed. The conformations of the *N*-methyl-and *N*-unsubstituted *cis*-trimethylene-, *cis*-tetramethylene-, and *cis*-pentamethylene-1,3-oxazinan-4-ones (**13**)—(**16**) were determined by ^1H and ^{13}C n.m.r. spectroscopy in solution. Good agreement was obtained with the earlier data established by *X*-ray diffraction analysis of the crystalline substances. The relative steric structure of the C-2 centre of chirality was also proved by d.n.O.e. measurements. It was found that the substituent at position 2 did not affect the conformation significantly.

In the course of systematic synthetic and stereochemical studies of bicyclic saturated and partially saturated fused-skeleton heterocyclic compounds we have prepared 1,3-heterocycles denoted by the general formula (**1**). Such compounds were *cis*- and *trans*-trimethylene-, tetramethylene-, and pentamethylene-tetrahydro-1,3-oxazine structural isomers,[2] the analogous 1,3-oxazin-2-ones[3,4] and 2-thiones.[5] and their *N*-substituted derivatives.[5,6] Trimethylene derivatives with *trans* structure were obtained only in the case of the 1,3-oxazin-2-ones and 2-thiones.[7] Similarly, tricyclic pyrimidinone derivatives of type (**2**) with different degrees of saturation and possible stereoisomers[8-10] were synthesized, and their conformations were studied by n.m.r. and *X*-ray diffraction analysis. Further compounds prepared were the 2-monosubstituted and 2,2-disubstituted 1,3-oxazinan-4-ones (**13**) and (**14**), including the *cis*-trimethylene and *cis*- and *trans*-pentamethylene homologues;[11,12] several of them had very favourable anti-inflammatory action.[12]



(**1**)



(**2**)

In the present work we report the synthesis of fused-skeleton *N*-methyl-1,3-oxazinan-4-ones (**15**) and (**16**), and comparative ^1H and ^{13}C n.m.r. spectroscopic studies of the steric structures of these compounds and those of the corresponding *N*-unsubstituted analogues (**13**) and (**14**). The synthesis of the latter two compounds was described earlier,[11,12] but their spectroscopic structure elucidation has not previously been reported.

As the steric structures of the 2-(*p*-chlorophenyl)-*cis*-trimethylene- (**13a**)[13] and *cis*-pentamethylene-1,3-oxazinan-4-one (**13c**)[14] derivatives had been determined earlier by *X*-ray diffraction, in the present work it was possible to compare the former solid-phase results with those obtained now by n.m.r. spectroscopy in solution.

(**3**) - (**12**) defined in Table 1

(**13**) (*cis*, R^1 = H) (**15**) (*cis*, R^1 = CH_3)
(**14**) (*trans*, R^1 = H) (**16**) (*trans*, R^1 = CH_3)
(a) n = 1, R^2 = C_6H_4Cl(*p*)
(b) n = 2, R^2 = C_6H_4Cl(*p*)
(c) n = 3, R^2 = C_6H_4Cl(*p*)
(d) n = 2, R^2 = H

Scheme. *Reagents:* i, $HCOC_6H_4Cl$(*p*); ii, HCOH

Syntheses.—The preparation of the *N*-substituted 1,3-oxazinan-4-ones was attempted in a way similar to that for the synthesis of the unsubstituted analogues. The *N*-methyl-2-hydroxycycloalkane-1-carboxamides (**3**)—(**8**) used as the starting compounds were prepared by treatment of the corresponding stereohomogeneous ethyl 2-hydroxycycloalkane-1-carboxylates[15,16] with methylamine. Carboxamides (**9**)—(**12**) were made by heating the *cis*- or *trans*-2-hydroxycyclohexane-1-carboxylic acids with the appropriate amine at 170 °C (Table 1).

Heating the *N*-methylcarboxamides (**3**)—(**8**) with *p*-chlorobenzaldehyde in dioxane led to acid-catalysed ring-closure (Scheme) in a yield of about 80% (Table 1). From the other *N*-substituted carboxamides (**9**)—(**12**) (the *N*-substituent being Ph, CH_2Ph, or CH_2CH_2Ph) under similar conditions, the starting material was recovered unchanged. *N*-Methyl-*trans*-2-hydroxycyclopentane-1-carboxamide (**4**) could not be cyclised to 3-methyl-*trans*-5,6-trimethylene-1,3-oxazinan-4-one either, in agreement with our earlier experiments with *trans*-1,3-bifunctional cyclopentane derivatives (see, *e.g.*, ref. 7).

N-Unsubstituted 2-hydroxycycloalkane-1-carboxamides reacted with paraformaldehyde to give methylene-bridged, bis-(4-oxo-1,3-oxazinan-3-yl)methane derivatives.[11] The corresponding reaction of the *N*-methylcarboxamides (**5**) and (**6**) gave, as expected, the oxazinanes (**15d**) and (**16d**) in high yield.

Structural Elucidation.—All compounds examined were racemates. The diagrams show only the enantiomer in which the

Table 1. Physical and analytical data of alicyclic *N*-substituted 2-hydroxycycloalkane-1-carboxamides (**3**)—(**12**) and *N*-methyloxazinanones (**15a**)—(**15d**) and (**16b**)—(**16d**)

Compound	Configuration	*n*	R^1	R^2	Crystallisation solvent	M.p. (°C)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H	Yield (%)
(3)	*cis*	1	Me	—	*a*	78—79[b]			$C_7H_{13}NO_2$			
(4)	*trans*	1	Me	—	benzene	75—77[c]			$C_7H_{13}NO_2$			
(5)[d]	*cis*	2	Me	—	*a*	68—70	61.2	9.7	$C_8H_{15}NO_2$	61.1	9.6	94
(6)[d]	*trans*	2	Me	—	*a*	149—150	61.2	9.8	$C_8H_{15}NO_2$	61.1	9.6	88
(7)	*cis*	3	Me	—	*a*	85—87	63.3	9.9	$C_9H_{17}NO_2$	61.1	10.0	83
(8)	*trans*	3	Me	—	*a*	88—91	62.3	10.1	$C_9H_{17}NO_2$	63.1	10.0	79
(9)	*cis*	2	Ph	—	ethyl acetate	200—201	71.1	7.9	$C_{13}H_{17}NO_2$	71.2	7.8	86
(10)	*trans*	2	Ph	—	ethyl acetate	179—181	71.4	7.5	$C_{13}H_{17}NO_2$	71.2	7.8	58
(11)	*cis*	2	CH_2Ph	—	ethanol–water	89—90[e]			$C_{14}H_{19}NO_2$			
(12)	*cis*	2	CH_2CH_2Ph	—	ethanol–water	121—123	72.7	8.7	$C_{15}H_{21}NO_2$	72.8	8.6	69
(15a)	*cis*	1	Me	$C_6H_4Cl(p)$	ethyl acetate	132—133	63.1	6.2	$C_{14}H_{16}ClNO_2$	63.3	6.1	83
(15b)	*cis*	2	Me	$C_6H_4Cl(p)$	di-isopropyl ether	174—175	64.2	6.8	$C_{15}H_{18}ClNO_2$	64.4	6.5	78
(15c)	*cis*	3	Me	$C_6H_4Cl(p)$	ethyl acetate	117—119	65.2	6.8	$C_{16}H_{20}ClNO_2$	65.4	6.9	80
(15d)	*cis*	2	Me	H		B.p. 130 °C (3×10^2 Pa)	63.7	7.8	$C_9H_{15}NO_2$	63.9	8.9	92
(16b)	*trans*	2	Me	$C_6H_4Cl(p)$	ethyl acetate	153—154	64.3	6.5	$C_{15}H_{18}ClNO_2$	64.4	6.5	80
(16c)	*trans*	3	Me	$C_6H_4Cl(p)$	di-isopropyl ether	77—79	65.4	6.8	$C_{16}H_{20}ClNO_2$	65.4	6.9	30
(16d)	*trans*	2	Me	H	n-hexane	81—83	63.9	8.9	$C_9H_{15}NO_2$	63.9	8.9	90

[a] Benzene–light petroleum. [b] Lit.,[7] 77—79 °C. [c] Lit.,[7] 76—77 °C. [d] These intermediates have been described before (L. Gera, G. Bernáth, and P. Sohár, *Acta Chim. Acad. Sci. Hung.*, 1980, **105**, 293) but no physical data were given. [e] Lit. (G. Bernáth, E. Csókási, I. Hevér, L. Gera, and K. Kovács, *Acta Chim. Acad. Sci. Hung.*, 1971, **70**, 271) 89—90 °C.

C-1 atom of the starting carboxamides, and consequently the C-5 atom in the oxazinones, has the *R* configuration.[17] The ring-closure, with aldehyde, of the 2-hydroxy-1-carboxamides, leading to the 2-monosubstituted 1,3-oxazinanones (**13**)—(**16**), results in the introduction of a new centre of chirality at position C-2; in principle, therefore, the formation of two diastereoisomers at each position might be expected. Actually, in the cyclisation reactions of *cis*- and *trans*-2-hydroxy-1-carboxamides the crude product in every case contained only a single detectable diastereoisomer. Both *trans* isomers A [*r*-5,*t*-2,*t*-6 (oxazine numbering)] and B (*r*-5, *c*-2,*t*-6), and also their *cis* counterparts C (*r*-5,*c*-2,*c*-6) and D (*r*-5,*t*-2,*c*-6), may exist in two stable conformations, in which the cyclohexane ring is present in a chair conformation and the hetero ring in either a twist or a boat conformation (Figures 1 and 2). Thus, in the determination of the configurations, the conformational relations must also be considered.

The principles of determining the steric structure of condensed oxazines by n.m.r. spectroscopy have been described in detail.[3,6] The presence of the planar amide group in the hetero ring results in a lower energy difference between the two relatively stable (twist and boat) conformations of the heterocycles. The 1,3-oxazinan-4-ones are therefore more flexible molecules than the 1,3-oxazinanes of type (**1**) investigated earlier, and the existence of their conformationally homogeneous systems cannot be expected.

The dioxan-4-one ring of the closely analogous *cis*- and *trans*-5,6-tetramethylene-1,3-dioxan-4-ones had a half-chair conformation. In this predominant conformation of the *cis* isomers the carbonyl group had an axial, and O-1 an equatorial, orientation relative to the cyclohexane ring.[18]

Concerning the ring-junction stereochemistry, the chemical shift and half-bandwidth of the 6-H signal is diagnostic. The shift is considerably greater and the width is smaller when 6-H has the quasi-equatorial orientation, corresponding to the relation generally characteristic for cyclohexane derivatives: $\delta_{H_{eq}} > \delta_{H_{ax}}$ or $^3J\,(H_{eq},H_{ax}) \approx {}^3J\,(H_{eq},H_{eq}) < {}^3J\,(H_{ax},H_{ax})$ (see, *e.g.*, refs. 19 and 20). Since 6-H is quasi-axial in the *trans* compounds and in the 'O-*out*' conformation of the *cis* isomers, whereas it is quasi-equatorial if the *cis* derivatives are in the 'O-*in*' conformation, the similar (or different) characteristics of the 6-H signals for the isomer pairs may allow differentiation between the 'O-*out*' and 'O-*in*' conformations of the *cis* isomers.

The tetramethylene derivatives give characteristically different 6-H signals for both the isomer pairs (**13b**), (**14b**) and (**15b**),

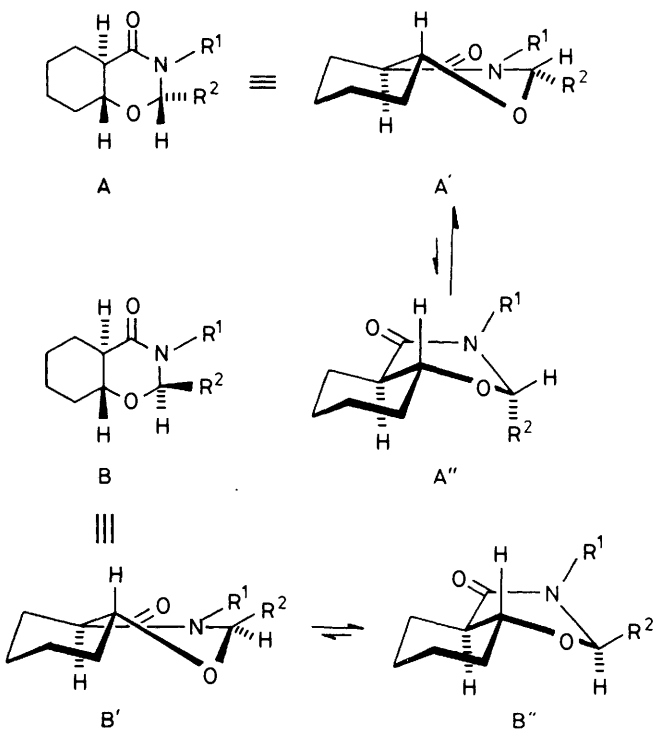


Figure 1.

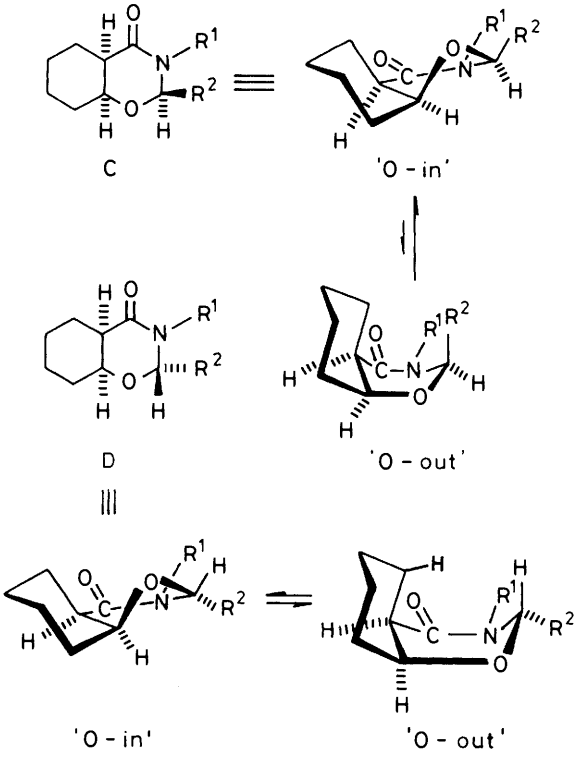


Figure 2.

C-2, since a 2-aryl substituent may affect the 6-H chemical shift, depending on its steric orientation, but it does not influence the couplings, *i.e.* the half-bandwidth. Consequently, the above data contain no information about the configuration at C-2.

Further evidence for the ring annelation and the 'O-*in*' conformation of the *cis* isomers is provided by the similar shifts of the signal of 5-H, which is quasi-axial in the *cis–trans* pairs, and by the unchanged half-bandwidth (25—30 Hz).

The 'O-*in*' conformation of the *cis* isomers with the D configuration is unfavourable, because of the quasi-axial orientation of the aryl substituent and the consequent steric hindrance between 6-H and the *ortho* hydrogens; the molecule cannot elude this hindrance, even in the boat ('O-*out*') conformation of the hetero ring, because then atoms 2-H and 10-H would approach each other to a distance of 1.1 Å.

When configuration C is considered, the 'O-*in*' conformation and the twist form of the oxazine ring generate a quasi-equatorial orientation for the aryl substituent, and this is therefore the most stable conformation of the *cis* isomers.

Attempts to synthesize the *trans* analogues of the *cis*-annelated cyclopentane analogues (**13a**), (**15a**) were unsuccessful, and thus the spectral data on the isomers could not be compared directly; however, the half-bandwidth and relatively large chemical shift of the 6-H signal (Table 2) indicate that, similar to the *cis*-tetramethylene derivatives, the 'O-*in*' conformation is preferred for (**13a**), (**15a**). The larger chemical shift and slight broadening of the signal as compared with those for the homologues (**13b**), (**15b**) are due to the reduced ring size. (The chemical shifts and vicinal coupling constants of the protons in the cyclopentane derivatives are higher than those

Table 2. I.r. and ^{1}H n.m.r. data for compounds (**13**)—(**16**)

	i.r. (cm^{-1}; KBr)		Chemical shifts (p.p.m.)								
Compound	ν_{NH} (broad)	$\nu_{C=O}$	2-H s (1 H)	5-H m (1 H)	$w_{\frac{1}{2}}$ (5-H)[a] (Hz)	6-H m (1 H)	$w_{\frac{1}{2}}$ (6-H)[a] (Hz)	CH_2 (7—11-H) m	NCH_3 s (3 H)	NH s (1 H)	ArH[b] m (4 H)
(**13a**)	3 200—2 700 (3 155, 3 050)	1 655	5.67	2.55	25	4.45	10	1.65 (1 H), 1.95 (4 H), 2.20 (1 H)	—	6.70	7.38
(**13b**)	3 160, 3 060	1 660	5.72	2.25	25	4.10	8	1.2—2.1 (8 H)	—	7.15	7.38
(**13c**)	3 160, 3 045	1 670	5.70	2.50	20	4.25	20	1.2—2.2 (10 H)	—	6.20	7.38
(**14b**)	3 180, 3 090	1 680	6.00	2.25[c]		3.45[d]	30	1.2 (3 H), 1.4 (1 H), 1.75 (2 H), 1.9 (1 H), 2.25 (2 H)[c]	—	7.35	7.39
(**14c**)	3 200—2 750	1 675	6.00	2.4[c]		3.50[d]	30	1.1—1.7 (8 H), 1.95 (1 H), 2.4 (2 H)[c]	—	8.20	7.38
(**15a**)	—	1 625	5.58	2.65	30	4.41	12	1.65 (1 H), 1.9 (4 H), 2.3 (1 H)	2.55	—	7.31, 7.38
(**15b**)	—	1 640	5.55	2.40	30	4.15	8	1.2—2.2 (8 H)	2.55	—	7.34, 7.40
(**15c**)	—	1 655	5.52	2.50	20	4.12	20	1.2—2.2 (10 H)	2.55	—	7.32, 7.39
(**15d**)	—	1 650	4.74[e] 4.80[e]	2.30	25	3.98	8	1.2—2.0 (8 H)	2.83	—	—
(**16b**)	—	1 645	5.61	2.30	30	3.65[d]	30	1.3 (4 H), 1.85 (2 H), 2.05 (1 H), 2.45 (1 H)	2.56	—	7.32, 7.39
(**16c**)	—	1 630	5.64	2.45[c]		3.75[d]	30		2.55[c]	—	7.35, 7.40
(**16d**)	—	1 640	4.74[e] 4.84[e]	2.40	30	3.45[d]	30	1.1 (2 H), 1.0—1.5 (4 H), 2.05 (2 H)	2.83	—	—

[a] Half-bandwidth; [b] AA'BB' multiplet (**15a**)—(**15c**), (**16a**)—(**16c**) coalesced to a singlet-like signal in the case of compounds (**13a**)—(**13c**) and (**14b**), (**14c**); [c] Overlapping signals; [d] 2 × *t*; [e] A or B part of an AB multiplet of 2 H intensity, J_{AB} 8 Hz.

(**16b**), respectively (Table 2). For the *cis* isomers (**13b**), (**15b**) the shift is greater (4.1—4.15 p.p.m.) and the half-bandwidth smaller (*ca.* 8 Hz) as compared with the *trans* pair (**14b**), (**16b**) (3.45—3.65 p.p.m. and *ca.* 30 Hz). Accordingly, the suggested *cis*- or *trans*-annelated structure of the isomer pairs can be regarded as proved, and so can the 'O-*in*' conformation (quasi-axial oxygen in relation to the cyclohexane ring, and therefore quasi-equatorial orientation of the carbonyl) in the *cis* isomers.

This statement holds true irrespective of the configuration at for the analogous cyclohexanes (see, *e.g.*, ref. 19*b*). The *X*-ray diffraction analysis[13] of (**13a**) gave evidence of a similar conformation in the solid phase.

The half-bandwidth of the 6-H signal of the *cis*-pentamethylene homologues (**13c**), (**15c**) is 20 Hz, which is approximately the average of the half-bandwidths for the isomer pairs containing a cyclohexane ring. It follows that in solution the 'O-*in*' and 'O-*out*' conformers are in equilibrium, the probabilities of their occurrence being about equal. In agreement with this, *X*-

Table 3. ^{13}C N.m.r. chemical shifts (p.p.m.) for compounds (**13**)—(**16**)

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	CH_3	C-1′	C-2′, -6′	C-3′, -5′	C-4′
(**13a**)	84.3	172.4	45.7	80.3	23.2	29.8	33.7	—	—	—	136.7	129.2	128.1	135.8
(**13b**)	84.7	173.4	43.0	73.1	26.6	20.2	24.9	30.1	—	—	137.5	129.0	128.2	135.5
(**13c**)	84.7	173.1	48.0	77.6	30.3	21.9	29.2	27.5	32.9	—	137.2	129.2	128.2	135.0
(**14b**)	81.6	172.2	46.5	73.1	25.2	24.3	24.7	32.5	—	—	137.9	129.1	128.1	135.3
(**14c**)	81.4	173.4	47.4	74.4	26.4	23.3	26.1	25.8	35.0	—	138.0	129.0	128.2	135.1
(**15a**)	89.8	170.7	46.9	79.6	22.8	29.7[a]	33.3	—	—	29.7[a]	136.4	129.0[b]	129.1[b]	135.7
(**15b**)	90.6	171.8	43.9	72.6	26.8	20.1	25.0	29.9	—	29.5	136.8	129.2[b]	129.3[b]	135.7
(**15c**)	89.8	171.7	48.8	76.0	30.1	21.3	29.3	27.2	32.8	29.8	136.5	128.9[b]	129.0[b]	135.5
(**15d**)	78.9	170.0	42.8	73.2	25.4	20.0	24.2	29.3	—	28.7	—	—	—	—
(**16b**)	90.6	170.2	46.8	77.8	25.4	24.3	25.3	32.3	—	29.7	137.0	129.0[b]	129.1[b]	135.6
(**16c**)	90.5	171.4	48.9	80.6	26.9	22.9	26.2	25.9	35.0	30.3	136.9	129.1[b]	129.2[b]	131.0
(**16d**)	79.8	169.2	46.7	79.1	29.4	24.3	25.1	32.3	—	29.4	—	—	—	—

[a] Two overlapping lines (confirmed by proton-coupling measurements). [b] Reversed assignment is also possible.

ray diffraction data[14] on (**13c**) indicated the isoclinal position of the oxygen atom in the solid phase.

X-Ray diffraction analysis supports the twist conformation of the hetero ring and the equatorial position of the C-2 phenyl substituent, in accord with the configuration of the C-2 atom derived from ^1H n.m.r. data, *i.e.* the C (*r*-5,*c*-2,*c*-6) diastereoisomer structure is confirmed.

The *trans*-annelated diastereoisomer A (*r*-5,*t*-2,*t*-6) is stable in the conformation A′ containing the phenyl group in a quasi-equatorial position and the oxazinanone ring in a twist form. The sterically unfavourable A″ conformer with a quasi-axial phenyl group attached to a twisted boat hetero ring can be ruled out. The unfavourable quasi-axial orientation of the phenyl group, however, may also be avoided by the flip of the oxazinane ring into the boat form (B″). For this reason the configuration of the *trans* isomers cannot be determined on the basis of ^1H n.m.r. measurements.

The ^{13}C n.m.r. data (Table 3), in agreement with the ^1H n.m.r. shifts, support the steric structures deduced above. The change in annelation is shown by the upfield shifts of the lines for the *cis* isomers (field effect).[21] Higher shielding is observed mainly for the C-8 and C-10 atoms, which are in 1,3-diaxial interaction with the quasi-axial oxygen, and for the annelated C-5 atom in the *cis* isomers, but in the *N*-methyl-substituted pair (**15b**), (**16b**) too the C-6 shift is smaller for (**15b**), evidently owing to the increased steric hindrance caused by the *N*-substituent. The fact that a significantly different C-6 shift is not observed for the isomers (**13b**), (**14b**) indicates that C-6 is also hindered in the *trans* isomers (**14b**). This renders structure A′ probable, *i.e.* the *S*-configuration at C-2, since in the A′ arrangement there is a 1,3-diaxial interaction between the 2-H_{ax} and 6-H_{ax} atoms, whereas in the B″ conformation an analogous interaction would operate between 5-H_{ax} and 2′-H_{ax}.

The suggested A′ structure of the *trans* isomers was supported in the case of (**14b**) by d.n.O.e. (differential nuclear Overhauser effect) measurements. When the values measured in the 'normal spectrum' are subtracted from the determined signal intensities of the double resonance (d.r.) spectrum (d.n.O.e.) (Figure 3a), the net spectrum will show only the signals whose intensities were affected by the d.r. experiment. When the 6-H signal is saturated, primarily the 2-H signal becomes more intense, and a simultaneous increase in intensity is also observed in the signals of the two cyclohexane hydrogens 8-H_{ax} and 10-H_{ax} in the 1,3-diaxial position (Figure 3b). In the opposite experiment, when the 2-H signal is saturated, with an increase of the 6-H signal, higher intensities are observed for the signals of the NH and aromatic protons (Figure 3c).

These experiments provide convincing evidence for structure A′, since in the A″ conformation and in any conformation of configuration B, atoms 2-H and 6-H would be distant from each other, no d.n.O.e. would appear and, in epimer B, the saturation of the 2-H signal would involve an increase in intensity of the 5-H signal.

It is to be noted that d.n.O.e. measurements on (**13b**) provide further evidence for the configuration C and 'O-*in*' conformation of the *cis* isomers. On saturation of the 2-H signal, increases in the 6-H and aromatic signals can be observed, while saturation of 6-H led to enhanced intensities of the 2-H and 5-H signals.

Experimental

M.p.s were determined with a Boetius micro melting point apparatus and are uncorrected. The physical properties of the prepared compounds are listed in Table 1.

The i.r. spectra were measured in KBr pellets on a SPECORD 75 (Jena, G.D.R.) grating spectrophotometer. The ^1H and ^{13}C n.m.r. spectra were recorded in $CDCl_3$ solution in 5 and 10 mm tubes, respectively, at room temperature on a Bruker WM-250 or WP 80 SY FT spectrometer at 250.13 and 20.14 MHz, respectively, using the ^2H peak of the solvent as the lock and tetramethylsilane as internal standard. The most important measuring parameters of the ^1H and ^{13}C spectra were as follows: spectral width 5 KHz; pulse width 1 and 3.5 μs (20° and 30° flip angle); acquisition time 1.64 s; number of scans 8 and 1 K—32.8 K; computer memory 16 K. Complete proton-noise decoupling (*ca.* 3 W) for the ^{13}C spectra and Lorentzian exponential multiplication for signal-to-noise enhancement were used (line width 0.7 and 1.0 Hz). Differential n.O.e. experiments were performed with the Bruker microprogramme No. 12.5 in the ASPECT 2000 pulse programmer. Gated decoupling to generate n.O.e. was used with a delay time of 5 s and a decoupling power of 50 mW; number of scans 32, dummy scans 2. Light petroleum refers to the fraction boiling in the range 55—65 °C.

N-*Methyl*-cis-2-*hydroxycycloheptane*-1-*carboxamide* (**7**).—Ethyl *cis*-2-hydroxycycloheptane-1-carboxylate[16] (9.3 g, 50 mmol) was kept at room temperature for 10 days in methanol (100 ml) containing 20% methylamine. After evaporation of the solvent, the oily residue was triturated with benzene, then with light petroleum, and the crystals which separated were filtered off. The product was purified as described in Table 1.

N-*Phenyl*-cis-2-*hydroxycyclohexane*-1-*carboxamide* (**9**).—*cis*-2-Hydroxycyclohexane-1-carboxylic acid[15] (1.44 g, 10 mmol) and aniline (3.72 g, 40 mmol) were heated for 2 h on an oil-bath

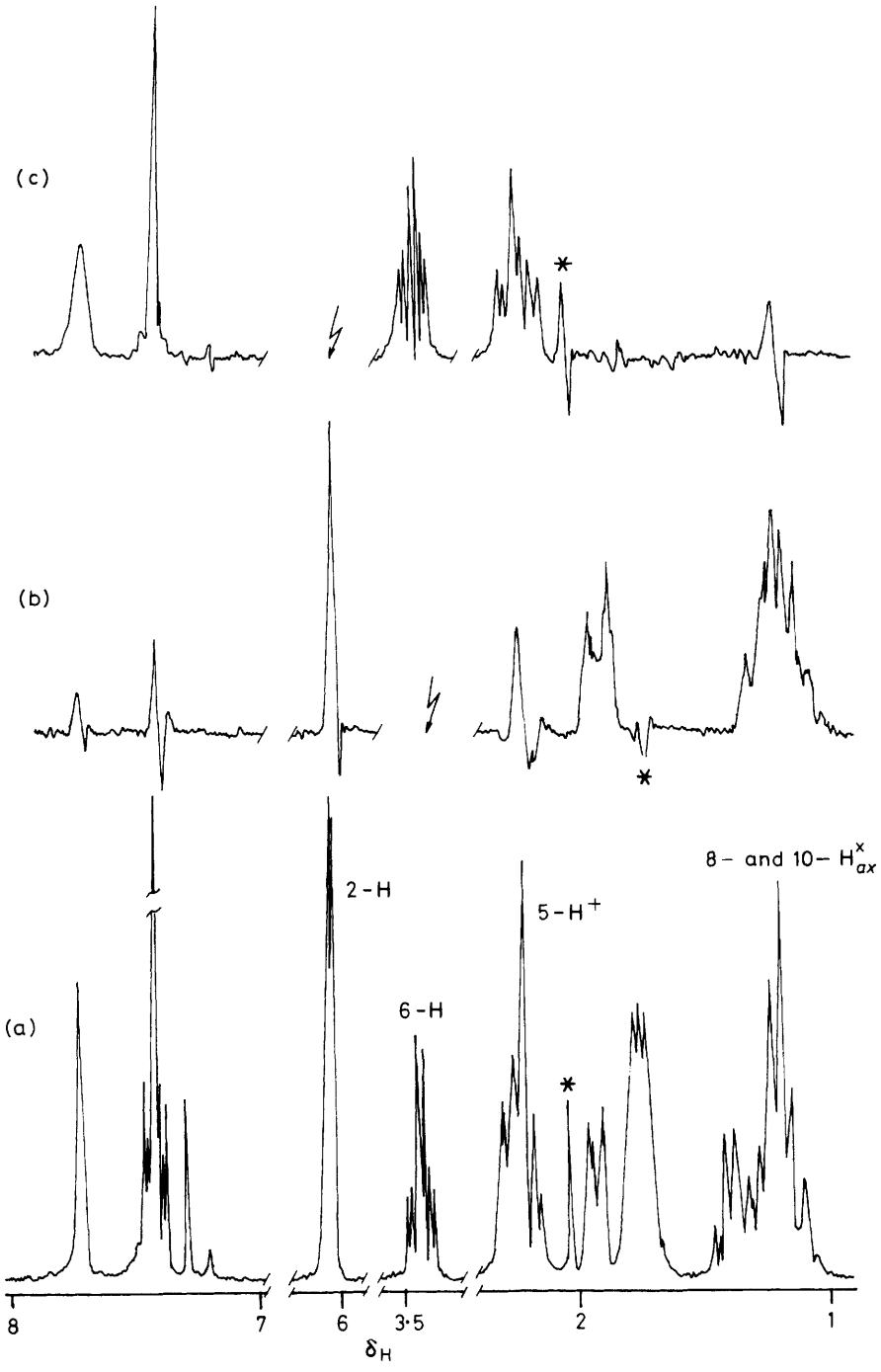


Figure 3. The ^{1}H n.m.r. spectrum (a) of compound (**14b**) and the d.n.O.e. experiment, with saturation of the 6-H (b) and the 2-H (c) signal, respectively. * Folded-back signal. $^+$ Overlapping signals of 5-H and 7-H_{eq} or 10-$_{eq}$. $^\times$ Overlapping signals of 7-, 8-, 9- and 10-H_{ax}

at 170 °C. After evaporation of the excess of aniline, the residue crystallised on trituration.

(r-5,c-2,c-6)-2-(4-*Chlorophenyl*)-3-*methyl*-5,6-*trimethylene*-2,3,5,6-*tetrahydro*-1,3-*oxazin*-4-*one* (**15a**).—*N*-Methyl-*cis*-2-hydroxycyclopentane-1-carboxamide (**3**) (1.43 g, 10 mmol) was refluxed with 4-chlorobenzaldehyde (1.55 g, 11 mmol) in dry dioxane (50 ml) in the presence of 1 drop of ethanolic hydrogen chloride catalyst for 20 h. The solution was concentrated to half of its volume, and water was added until opalescence began to appear. Next day the crystalline product (**15a**) was filtered off and purified as described in Table 1.

3-*Methyl*-trans-5,6-*tetramethylene*-2,3,5,6-*tetrahydro*-1,3-*oxazin*-4-*one* (**16d**).—*N*-Methyl-*trans*-2-hydroxycyclohexane-1-carboxamide (**6**) (1.57 g, 10 mmol) and paraformaldehyde (1 g) were refluxed for 10 h in dry dioxane in the presence of 1 drop of conc. sulphuric acid. The solution was then evaporated to dryness and the residue was dissolved in ether (3 × 30 ml). Evaporation of the ethereal solution gave the crystalline product (**16d**), purified as described in Table 1.

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