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STEREOCHEMICAL STUDIES – XVII[1]

CYCLIC AMINOALCOHOLS AND RELATED COMPOUNDS – IX[1] SYNTHESIS AND NMR STUDY OF STEREOISOMERIC *CIS*- AND *TRANS*-TETRAMETHYLENE- AND PENTAMETHYLENE-1,3-OXAZINE-2-ONES

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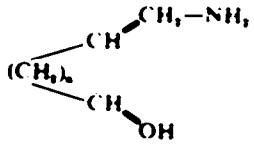
Abstract – Isomeric tetramethylene- and pentamethylene-1,3-oxazine-2-ones (9–12 and 13–16) have been synthesized, derived from *cis*- and *trans*-2-aminomethylcyclohexanol (1, 2), *cis*- and *trans*-2-hydroxymethylcyclohexylamine (3, 4) and from the corresponding cycloheptane analogues (5–8), respectively. The stereospecific synthesis of the aminoalcohols 5–8 is described. A comparative NMR analysis of 13–16 and the tetramethylene analogues (9–12) is given.

Conformational studies on saturated heterocycles are in the foreground of recent research.[2] Therefore, we prepared and investigated some perhydrogenated heterocycles from the model compounds of our recent stereochemical studies[3–5] on cyclic 1,3-aminoalcohols. In former experiments, *cis*- and *trans*-2-aminomethylcyclohexanol (1, 2) and *cis*- and *trans*-2-hydroxymethylcyclohexylamine (3, 4) were converted to tetrahydrooxazines[6] related to the bicyclic transition state of the N → O acyl migration reaction[3, 6] of N-benzoyl derivatives of 1–4. IR and NMR analysis of the tetramethylene-tetrahydro-1,3-oxazine-2-ones (9–12) derived from 1–4 were discussed.[7, 8] The present paper describes the synthesis of 9–16, and the NMR analysis of the pentamethylene analogous (13–16).

The stereospecific synthesis of 1–4 was published[9] earlier. The cycloheptane analogues 5–8 were prepared in a similar way by LAH reduction of *cis*- and *trans*-2-hydroxycycloheptanecarboxamide (17, 18) and *cis*- and *trans*-2-aminocycloheptanecarboxylic acid (21, 23), respectively (Chart 3). Compounds 17 and 18 were synthesized, from the corresponding esters,[10] 21 was made by Hofmann degradation of the monoamide 20 obtained from the anhydride[11] 19; and 23 was prepared by ammonia addition to 1-cycloheptene-1-carboxylic acid (22) as described[9] for 1-cyclohexene-1-carboxylic acid.



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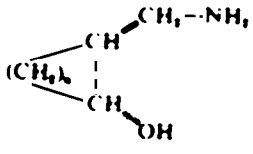
n = 5 5



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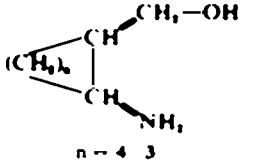

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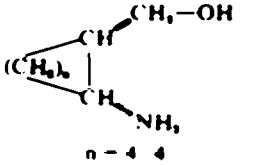
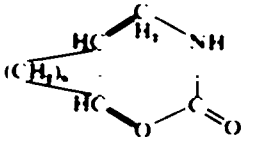
n = 5 7



n = 4 4
n = 5 8

CHART 1



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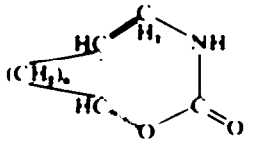
n = 5 13



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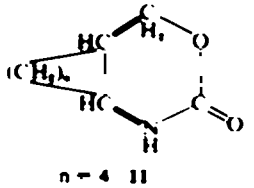
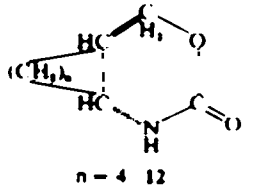
n = 5 14



n = 4 11
n = 5 15



n = 4 12
n = 5 16

CHART 2

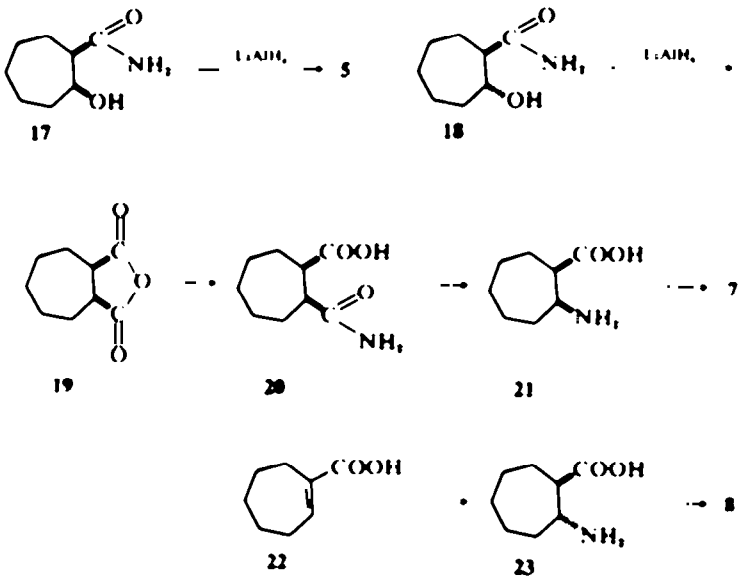


CHART 3

In preparing the oxazinones **9–16** the process of Mousseron *et al.*[11] was applied, though other methods[12–14] were also taken into consideration. Compound **10** was prepared earlier by Mousseron *et al.*;[11] but their product reported with m.p. 180–181° must have been a mixture of *cis* and *trans* isomers, because the starting material, *trans*-2-aminomethylcyclohexanol[15] obtained from 2-cyanocyclohexanol (in spite of recent supporting data[16]) was, as we pointed out,[9] a *trans–cis* isomeric mixture (**2** and **1**). Our above statement has been confirmed in a very recent paper by Schwartz *et al.*[17] For spectroscopically stereohomogeneous **10**, we found a m.p. of 185.5–186°.

The IR and NMR data[9] of **9–12** are consistent with the structures. NMR measurements also permitted the elucidation of the conformation of these compounds. While in the *trans* isomers both the methylene group of the hetero ring and the NH group (or O atom) must be *equatorial*, in the *cis* isomers (**9**, **11**) two conformations are possible, with both rings in chair form, which differ in the *equatorial* or *axial* orientation of the methylene group and the O atom (**9a**, **9b**) (or the NH group, **11a**, **11b**) (Strictly speaking, the heterocycle is somewhat distorted in these compounds, due to sp^2 C atom, the substituents are thus nearly *pseudo-equatorial* and *pseudo-axial*) (Chart 4). It follows from the NMR data[9] that in the *cis* isomers the methylene group of the hetero ring is *equatorial*, while the hetero atom is *axial* (**9a**, **11a**).

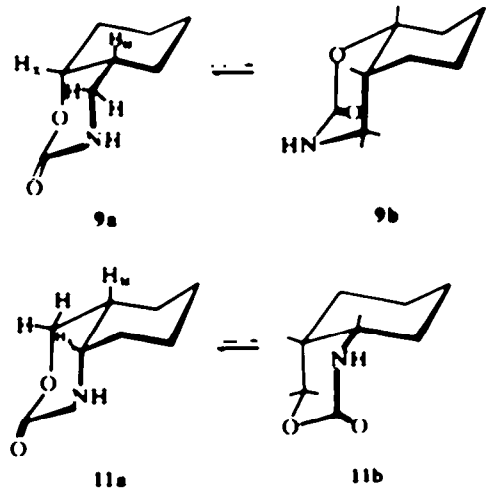


CHART 4

The cycloheptane isomers **13–16** have spectral parameters (Table 1) very similar to the cyclohexane derivatives[9] **9–12**, showing that the conformational relations are analogous in both series. Certain differences are still observable. The chemical shift differences of the X proton are greater for the *cis–trans* pairs in the case of compounds **11** and **12** (0·77), than for the cycloheptane analogues **15** and **16** (0·47).

In the case of the **11–15** pair, every conformation-dependent NMR parameter becomes slightly changed. It is characteristic that the width of the δX signal is greater for the *cis* isomer **15** (16 Hz) than for **11** (10 Hz). The same effect can be observed in the case of compounds **9** and **13** (8 Hz and 12 Hz, respectively).

From these results the conclusion can be drawn that the conformational equilibrium which is completely shifted towards conformation **a** in

Table 1. IR and NMR data of *cis* and *trans* 5,6-pentamethylene-1,3-tetrahydrooxazine-2-one (13, 14) and of *cis*- and *trans*-4,5-pentamethylene-1,3-tetrahydrooxazine-2-one (15, 16)

Compound	13	14	15	16
Wave number of IR spectra in cm^{-1}				
νNH	3280	3240, 3120	3230, 3120	3240, 3110
$\nu_{C=O}$ (urethane)	1690	1700	1695	1695
NMR data 1. Chemical shifts in ppm				
δH_A	3.47	3.30	4.13	4.17
δH_B	3.13	2.99	4.00	3.88
δH_X	4.60	4.00	3.67	3.2
δH_M + $4CH_2$	70–140°	70–130°	60–150°	70–130°
δNH	6.85	6.95	6.95	7.1
2. Coupling constants in Hz				
J_{AB}	11.0	11.0	11.0	11.0
J_{AX}	5.0	5.0	4.5	5.0
J_{BX}	3.0	11.0	6.5	11.0
width of the signal δX[a]	12	23	16	24

[a] Line width in Hz
[b] Increasing with J_{BX}

Table 2. M.ps and analytical data

No.	M.p.	Formula	Calc % C	Calc % H	Calc % N	Found % C	Found % H	Found % N	Note
5	170	$C_9H_{16}ClNO$	53.47	10.10		53.21	9.70		*a*
6	132	$C_9H_{16}ClNO$	53.47	10.10		53.10	10.43		*b*
7	149–150	$C_9H_{16}ClNO$	53.47	10.10		53.63	10.18		*b*
8	103–104	$C_9H_{16}ClNO$	53.47	10.10		53.59	10.50		*c*
9	141–142	$C_9H_{15}NO_2$	61.91	8.44	9.03	61.84	8.43	8.94	
10	185.5–186	$C_9H_{15}NO_2$	61.91	8.44	9.03	61.98	8.43	8.83	*d*
11	113–115	$C_9H_{15}NO_2$	61.91	8.44	9.03	61.64	8.78	8.71	
12	167–68.5	$C_9H_{15}NO_2$	61.91	8.44	9.03	61.98	8.66	9.27	
13	131–132	$C_9H_{17}NO_2$	63.88	8.93	8.28	63.74	9.21	8.33	
14	103–104	$C_9H_{17}NO_2$	63.88	8.93	8.28	63.70	8.94	8.66	
15	112–112.5	$C_9H_{17}NO_2$	63.88	8.93	8.28	63.47	9.04	8.20	
16	115–116	$C_9H_{17}NO_2$	63.88	8.93	8.28	63.60	9.05	8.29	
17	107–108	$C_{11}H_{19}NO_2$	61.12	9.63	8.91	61.05	9.72	8.67	*e*
18	127–128	$C_{11}H_{19}NO_2$	61.12	9.63	8.91	61.12	9.87	8.77	*e*
20	125–130	$C_{11}H_{21}NO_2$	58.36	8.16	7.56	58.27	7.83	7.27	*f*
21	242–243	$C_{11}H_{19}NO_2$	61.12	9.62	8.91	61.07	9.80	9.04	
23	282–285	$C_{11}H_{19}NO_2$	61.12	9.62	8.91	61.05	9.63	8.69	*f*

[a] Hydrochloride. Cl⁻: calc 19.73, found 19.73%
[b] Hydrochloride
[c] Hydrochloride. Cl⁻: calc 19.73, found 19.68%
[d] Lit.[11] m.p. 180–181°, see text
[e] White plates from toluene
[f] M.p. with decomposition

compounds 9 and 11, is changed in the case of compounds 13 and 15 to favour the conformers b. This may be due to the greater flexibility of the cycloheptane ring,[10, 11] also resulting in a diminishing difference in other properties of 1,2-disubstituted cycloheptanes.

EXPERIMENTAL

M.ps were determined on a Boetius apparatus, and are uncorrected. IR spectra were recorded with a Zeiss UR-10 (JENA) spectrometer in KBr pellets. NMR spectra were taken at room temp in 10% $CDCl_3$ solns on a VARIAN A-60D spectrometer, chemical shifts are reported in δ values relative to TMS as an internal standard

M.ps and analytical data of the new compounds are given in Table 2. The aminoalcohols 5–8 were prepared according to the method[9] described for the cyclohexane analogues 1–4 (Text and Chart 3) and were characterized as hydrochlorides. The derivatives 8–16 were synthesized applying the procedure of Mousseron *et al.*[11] slightly modified as follows.

cis-5,6-*Pentamethylenetetrahydro*-1,3-*oxazine*-2-*one* (13). 4·1 g (0·0283 mole) 5 and 8·2 g (0·13 mole) urea was taken up in 200 ml abs EtOH/HCl soln, the mixture was evaporated to dryness and kept at 170° (bath temp) for 30 min then at 200° for 1 hr. The product was powdered and refluxed with abs $CHCl_3$ (3 × 50 ml). After filtration and evaporation, the yellow residue was chromatographed on Al_2O_3 (50 g, activity II) (solvent) light petroleum (60–80°)-benzene-$CHCl_3$ mixtures of increasing concentrations). The fractions were checked with TLC (silicagel, benzene–EtOH 9:1 developer, I_2 visualization). 3·55 g (78%) was obtained, m.p. 129–131°; after repeated recrystallization from $CHCl_3$-light petroleum (60–80°) m.p. 131–132°. Analytical data: Table 2.

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