Saturated Heterocycles. Part 216 [1]. Synthesis, Structure and Ring Opening of *trans*-Perhydro-1,4-benzoxazepin-3-one Derivatives

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trans-Perhydro-1,4-benzoxazepin-3-ones **2a-e** were synthesized and transformed to condensed-skeleton perhydro-*trans*-1,4-benzoxazepines **3a,b**, the thiones **4a,b**, the urea derivatives **5a,b**, and *N*-acylated compounds **6a-e**. Compounds **6b,d** were ring-opened by hydrochloric acid in ethanol to yield *trans*-2-(1-carbethoxyethoxy)-1-acylaminomethylcyclohexane derivatives **7b,d**. The ^{1}H- and ^{13}C-nmr investigation and X-ray analysis of **5b** and **6c,d** proved that the expected *N*-acylated derivatives were formed and that both rings of the *trans* anellated compounds have a chair conformation.

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Introduction.

Various *cis* and *trans* condensed-skeleton dihydro- and tetrahydro-1,3-oxazines [2-5] and 1,3-thiazines [6] were synthesized earlier with the aim of comparative studies of their steric structures, reactions, stabilities and pharmacological activities [7]. To continue this work, we have now synthesized *trans*-1,4-oxazepin-3-ones condensed with cyclohexane, as perhydrogenated oxo analogues of the anxiolytic benzodiazepines [8], suitable for receptor subtype studies [9]. Oxazepines [10] and some aralkyl-substituted cyclopentane-condensed oxazepines were synthesized earlier and studied [11]. Benzoxazepinediones having the nitrogen and oxygen atoms in different positions are reported to be of medicinal importance [12-16].

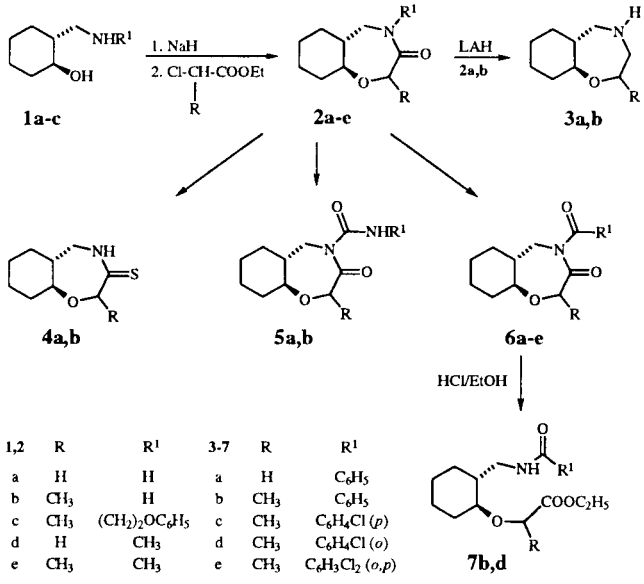
Synthesis.

trans-2-Aminomethylcyclohexanol **1a** and its *N*-substituted derivatives **1b,c** [4,5] were treated in benzene with sodium hydride and ethyl chloroacetate or ethyl 2-chloropropionate to yield *trans*-perhydro-1,4-benzoxazepin-3-ones **2a-e** (Scheme 1, Table 1). The aminoalcohols reacted with ethyl 2-chloropropionate to yield diastereomer pairs on cyclization, as a result of formation of the C2 chiral center [17]. However, in all cases only the major diastereomers were isolated because the minor components were lost during the work-up processes.

The oxo function of **2a,b** was reduced with lithium aluminium hydride (LAH) to furnish *trans*-perhydro-1,4-benzoxazepines **3a,b** (Scheme 1, Table 1). Compounds **2a,b** were transformed to the thioxo derivatives **4a,b** with phosphorus(V)sulphide in pyridine.

Of the two theoretically possible (*O*- or *N*-acyl) products, acylation furnished only the *N*-acyl derivatives [18]. Compounds **2a,b** reacted readily with phenyl isocyanate to form *N*-substituted urea derivatives **5a,b**. Similarly, *N*-acylated derivatives **6a-e** were formed by reacting **2a,b** with aromatic acid chlorides. For cyclic imides, the for-

Scheme 1



1,2	R	R¹	3-7	R	R¹
a	H	H	a	H	C_6H_5
b	CH_3	H	b	CH_3	C_6H_5
c	CH_3	$(CH_2)_2OC_6H_5$	c	CH_3	C_6H_4Cl (*p*)
d	H	CH_3	d	CH_3	C_6H_4Cl (*o*)
e	CH_3	CH_3	e	CH_3	$C_6H_3Cl_2$ (*o,p*)

Table 1

Physical and Analytical Data on Products

Compound	R^1	R^2	R^3	Formula MW	Mp Solvent	Analysis % Calcd./Found C	H	N	Yield %
2a	H	H		$C_9H_{15}NO_2$ 169.23	169-171 acetone	63.88 63.89	8.93 9.11	8.28 8.04	35
2b	H	CH_3		$C_{10}H_{17}NO_2$ 183.25	208-209 ethanol	65.54 65.34	9.35 9.58	7.64 7.90	37
2c	CH_3	H		$C_{10}H_{17}NO_2$ 183.25	86-89 *n*-hexane-acetone	65.54 65.28	9.35 9.56	7.64 7.62	39
2d	CH_3	CH_3		$C_{11}H_{19}NO_2$ 197.28	95-97 ether	66.97 66.66	9 71 9.97	7.10 7.14	47
2e	$(CH_2)_2OC_6H_5$	CH_3		$C_{18}H_{25}NO_3$ 303.41	113-114 ethanol-water	71.26 71.20	8.31 8.43	4.62 4.88	11
3a [a]	H	H		$C_9H_{18}ClNO$ 191.69	182-185 dec ethanol-ether	56.39 55.91	9.46 9.26	7.31 7.39	91
3b [b]	H	CH_3		$C_{10}H_{20}ClNO$ 205.73	122-123 ethanol-ether	58.38 57.98	9.80 10.20	6.81 6.98	92
4a [c]	H	H		$C_9H_{15}NOS$ 185.28	195-197 ethanol	58.34 58.33	8.16 7.87	7.56 7.45	76
4b [d]	H	CH_3		$C_{10}H_{17}NOS$ 199.32	150-152 ethanol-water	60.26 60.64	8.60 9.00	7.03 6.97	81
5a	H	H	C_6H_5	$C_{16}H_{20}N_2O_3$ 288.35	129-130 ether	66.65 66.98	6.99 7.30	9.72 10.00	89
5b	H	CH_3	C_6H_5	$C_{17}H_{22}N_2O_3$ 302.38	128-129 ether	67.53 67.43	7.33 7.55	9.26 9.50	88
6a	–	CH_3	C_6H_5	$C_{17}H_{21}NO_3$ 287.36	126-127 ether	71.06 71.20	7.37 7.51	4.87 4.90	70
6b	–	CH_3	$C_6H_4Cl(p)$	$C_{17}H_{20}ClNO_3$ 321.81	132-133 ethanol	63.45 63.54	6.26 6.61	4.35 3.97	73
6c	–	CH_3	$C_6H_4Cl(o)$	$C_{17}H_{20}ClNO_3$ 321.81	133-135 ethanol	63.45 63.71	6.26 6.60	4.35 4.35	69
6d	–	CH_3	$C_6H_3Cl_2(o,p)$	$C_{17}H_{19}Cl_2NO_3$ 356.25	122-123 ethanol	57.32 57.35	5.38 5.55	3.93 4.08	74
6e	–	H	C_6H_5	$C_{16}H_{19}NO_3$ 273.34	114-115 methanol	70.31 70.42	7.01 7.15	5.12 5.30	70
7b	–	CH_3	C_6H_5	$C_{19}H_{27}NO_4$ 333.43	72-73 methanol	68.44 68.25	8.16 8.07	4.20 4.12	47
7d	–	CH_3	$C_6H_4Cl(o)$	$C_{19}H_{26}ClNO_4$ 367.88	56-58 methanol	62.03 61.83	7.12 7.01	3.81 3.64	53

[a] Hydrochloride. [b] Picrate. [c] Calcd. S, 16.09. Found: S, 16.41%. [d] Calcd. S, 17.31. Found: S, 17.58%

mation of both *N*- and *O*-acylated products and their mixtures has been reported [19]. $O \rightarrow N$-Acyl migrations have also been detected under different conditions [20]. Detectable amounts of *O*-acylated isomers were not observed in our case.

Two products, **6b,d**, were treated with hydrochloric acid in ethanol; *trans*-2-(1-carbethoxyethoxy)-1-acylaminomethylcyclohexane derivatives **7b,d** were obtained by the facile opening of the heterocyclic ring, indicating the expected and stated position of the acyl group (Scheme 1, Table 1). Because of the possibility of acyl migration in this reaction, structural determinations were performed by ir, ^{1}H- and ^{13}C-nmr spectroscopy, and for **5b** and **6c,d** by X-ray diffraction.

Stereostructures. NMR Spectroscopic Studies.

Characteristic spectroscopic data (ir frequencies, ^{1}H- and ^{13}C-nmr chemical shifts and proton-proton coupling constants) of **2-7** are listed in Tables 2 and 3. The spectral data confirming the proposed structures do not require any particular explanation and we therefore make only the following remarks.

The ir carbonyl frequencies (< 1720 cm^{-1}) support the imide (*N*-acyl) structures for **5a,b** and **6a-e**. The enolic ester-type *O*-acyl analogues with a -N=C-O-CO moiety would give a significantly higher carbonyl frequency of about 1760 cm^{-1} [21]. The very high chemical shift difference of the 5-methylene hydrogens (*ca.* 1.3 ppm for compounds of types **5** and **6**, and about 0.4 ppm for derivatives **2-4**) is in accord with the imide structure, and is a consequence of the coplanar arrangement of H-5 *eq* and the side-chain carbonyl group (high downfield shift of the H-5 *eq* signal due to anisotropic effect of the latter [22a]).

In the preferred conformation of these compounds, both

Table 2

^{1}H-NMR Data (Chemical Shifts in δ, δ_{TMS} = 0 ppm, Coupling Constants in Hz) on **2a-e**, **3a,b**, **4a,b**, **5a,b**, **6a-e** and **7b,d** in $CDCl_3$ Solution at 250 MHz and Characteristic IR-Frequencies (in cm^{-1}) in KBr Discs [a,b]

Compound	CH_2/CH_3CH (2) (2H/3+1H) [c]		NCH_2 (5) (2 x 1H) [d]		CH (9a) *m* (1H) [e]	ArH (side-chain) 1-3 signal (3-5H)	NH/NMe NCH_2 [f]	ν NH band	amide-I band	ν C-O band
2a	4.14	4.25 [g]	2.98	~3.2 [h]	~3.2 [h]		~7.15	3225	1659	1105
2b	1.36	4.15	2.98	3.25 [h]	~3.25 [h]		~6.7	3275	1664	1105
2c	1.35	4.20	3.22	3.65 [h]	~3.2	6.85 [i] 6.95 [j] 7.30 [k]	4.02 [l]		1661	1101
2d	4.17	4.31	2.92	3.55	~3.10		3.00		1639	1111
2e	1.36	4.22	2.92	3.61	3.20		3.02		1647	1115
3a	3.65	3.89	2.52	~3.0 [h]	~3.0 [h]		~2.1	~3320		1117
3b	1.14	3.75	2.52	~2.95 [h]	3.13		~2.0	~3250		1090
4a	4.36	4.75 [g]	~3.15 [h]	3.37	3.15 [h]		~9.1	3163	1555	1076
4b	1.54	4.32	3.18	3.47	3.35		~9.15	3180	1549	1086
5a	4.45		~3.2 [h]	4.66	~3.2 [h]	7.10 [j] 7.32 [k] 7.50 [i]	~11.2	3250	1701 [m]	1111
5b	1.41	4.49	~3.3 [h]	4.68	~3.3 [h]	7.09 [j] 7.32 [k] 7.52 [i]	11.35	3230	1699 [m]	1140
6a	4.30	4.48 [h]	~3.25 [n]	4.48 [h]	~3.25 [n]	~7.4 [o] 7.60 [i]			1716 [m]	1110
6b	1.36	4.35	3.35 [h]	4.45	~3.35 [h]	7.38 [k] 7.48 [j] 7.57 [i]			1686	1109
6c	1.36	4.35	3.30 [h]	4.42	~3.30 [h]	7.35 [p] 7.50 [p]			1686	1101
6d	1.31	4.37	3.25 [h]	4.67	~3.25 [h]	7.2-7.4 [o]			1720 [m]	1111
6e	1.33	4.37	3.33 [h]	4.65	~3.3 [h]	7.20 [r] 7.28 [s] 7.37 [t]			1718 [m]	1101
7b	1.41	~4.25 [h]	3.30	3.86	3.15	7.35-7.50 [o] 7.90 [i]	~8.15	3373	1642	1130
7d	1.33	4.16	3.41	3.80	3.12	7.25-7.40 [o] 7.58 [u]	~7.70	3350	1664	1123

[a] Further ^{1}H-nmr signals: CH_3 (3H, Et): 1.28 (**7b**), 1.21 (**7d**), t (J = 7.0); OCH_2 (2H, side-chain): 4.15 m (**2c**), ~4.25 [h] qa (**7b**), ~4.09 qa (**7d**); NCH_2 (Pos 3): ~3.0 [h] m (2H) for **3a**, 2.66 dd (J = 13.8 and 8.1) and ~2.95 [h] m (1H) for **3b**; CH_2 (Pos 6-9) + CH (Pos 5a): 0.9-2.1 unresolved, partly overlapping m's of 9H total intensity. [b] IR ester band: 1749 (**7b**), 1735 (**7d**) [c] AB-type spectrum (2 x d) for **2a,d**, **4a** and **6a** (J = 14.5, 14.2, 14.7 and 16.3), A_3X multiplets (d + qa) for **2b,c,e**, **5b**, **6b,c** (J = 6.6), **4b**, **6d,e** (J = 6.4) and **7b,d** (J = 6.9), AB/A_3B part of an ABXY/A_3BXYspin system (2 xm/d + m) for **3a/3b** [J(A,B) = 6.3 for **3b**] and A_2 singlet (2H) for **5a**. [d] Upfield signal ddd (J ±0.2: 14.7, 7.5, 2.3 for **2a,b** and **4b**, 13.5, 7.0 and 5.0 for **7b,d**), dd (J ±0.2: 15.0 and 1.7 for **2c-e**, 13.9 and 9.1 for **3a**, 14.0 and 8.2 for **3b**, 14.9 and 10.5 for **5b** and **6b-e**), downfield signal dd (J ±0.2: 15.0 and 10.0 for **2d,e**, 15.0 and 1.7 for **5b** and **6a-e**), ddd (J = 14.5, 10.4 and 3.8 for **4a**, 14.6, 10.1 and 4.6 for **4b**, 13.5, 7.5 and 2.8 for **7b**, 13.5, 7.1 and 3.3 for **7d**), d (J = 15.0) for **5a**. [e] Half signal width ~30 Hz for **2d,e**, **3b**, **4a,b**, dt for **7b,d** (J = 9.9 and 4.1). [f] NH, broad signal (1H) for **2a,b-5a,b**, broadened t for **7b,d**, NCH_3, s (3H) for **2d,e**; NCH_2 (side-chain) for **2c**, 2 xm (2 x 1H), one of the two m's in overlap with the NCH_2 (Pos 5) signal at 3.65 ppm. [g] Further split by 1.7 Hz to dd (due to long-range coupling with H-9a). [h,n] Overlapping signals. [i] H-2',6' (phenyl), dd or coalesced to ~d (2H). [j] H-4' (phenyl) dt or ~t (1H). [k] H-3',5' (phenyl), dt or ~t (2H). [l] Intensity: 1H. [m] Split band pair with a second maximum at 1663 for **5a** and at 1674 for **5b** (as a shoulder) and for **6a,d,e**. [o] Overlapping m's of 3/4H total intensity (**6a**, **7b,d/6d**). [p] A or B part ~d (2H) of an AA'BB' spin system, J = 8.5 (δ H-2',6' > δ H-3',5'). [r] H-6, d (1H, J = 8.3). [s] H-5, dd (1H). [t] H-3, d (1H, J = 1.8). [u] H-6, dd (1H).

the cyclohexane and the heterocyclic rings have a chair form with C9 and the N4-CO(3) amide group out of plane. This conformation is the most favorable one, because of the possibility of strainless to incorparation of the lactam moiety into the condensed skeleton. This stereostructure is supported by the following facts:

a) The H-5 *ax*, H-5a and H-5 *eq*, H-5a vicinal couplings are characteristically different (7-10 and 1.5-3.5 Hz) due to the dihedral angles of *ca.* 170° and 70°.

b) The half width of the H-9a signal is about 30 Hz, proving two *diaxial* interactions for H-9a with the neighbouring vicinal H atoms.

c) The chemical shifts of the 6-9-methylene carbons in the cyclohexane ring are practically the same as in the cyclohexane-5,6-*trans*-condensed 2-phenylimino-1,3-oxazines, which have very similar structures [23], while there are significant differences between the former shifts and those measured for the *cis* analogues of the latter compounds. (The mean shifts of C5-9 in **4-6** are 29.2, 25.1, 24.7 and 33.2 ppm; the corresponding data for *cis*- and *trans*-phenylimine analogues are as follows: *cis*: 25.5, 24.0, 20.2 and 29.4 ppm; *trans*: 28.3, 25.1, 24.1 and 31.5 ppm [23]).

The 2-methyl group is *equatorial* and *cis* to H-5a (*trans* to H-9a). This follows from the data below:

a) There are only small differences in the carbon chemical shifts of C2,5,9a for 2-unsubstituted and 2-methyl-substituted pairs (types **a** and **b**, *etc.*). For a reversed C2 configuration (2*S**, 5a*R**, 9a*S** stereostructure instead of 2*R**, 5a*R**, 9a*S**), the field effect [24] would be manifested in significant upfield shifts of the C2,5,9a lines.

b) In the ^{1}H-nmr spectra of the 2-methyl derivatives, the chemical shift of H-2 *ax* is practically unchanged relative to that for the 2-unsubstituted counterpart. The higher shift (due to the anisotropic neighbouring effect of the coplanar carbonyl [22a] or thiocarbonyl [22b]) of H-2 *eq* (*cis* to H-5a) is absent in the 2-methyl compounds.

Determination of the Structure of **6c** by X-ray Diffraction.

The molecular geometry of **6c** (depicted in Figure 1) was computed from the final fractional atomic coordinates (Table 4). Bond distances and angles are given in

Table 3

^{13}C-NMR Chemical Shifts (δ_{TMS} = 0 ppm) for **2-7** in $CDCl_3$ Solution at 20.14 MHz [a,b]

Compound	C-2	C=O [c] (Pos 3)	C-5	C-5a	C-6	C-7,8		C-9	C-9a	CH_3 (Pos 2)
2a	72.5	176.3	47.9	45.4	29.3	24.9	25.2	33.0	88.3	
2b	75.0	176.6	47.6	45.3	29.2	25.1	25.3	33.5	88.0	17.2
2c	73.9	172.6	55.3	43.3	28.8	24.2	24.7	32.7	86.6	17 1
3a	69.5	49.9	54.8	48.6	30.1	24.8	25.1	33.6	83.6	
3b	75.8	56.7	54.4	48.9	30.1	24.8	25.1	33.7	83.1	20.0
4a	78.1	206.5	52.1	44.0	29.2	24.7	25.0	32.9	88.2	
4b	77.3	209.5	51.1	43.7	29.0	24.9	25.2	33.2	87.5	21.0
5a	74.7	176.1	48.3	44.7	29.4	24.8	25.2	32.8	88.6	
5b	75.5	177.1	47.6	44.7	29.3	24.9	25.3	33.2	88.2	17.5
6a	74.1	176.5	48.5	45.8	29.1	24.6	24.9	32.8	89.3	
6b	77.0	176.7	48.7	45.5	28.8	24.6	24.9	33.1	88.4	17.5
6c	77.0	176.8	48.8	45.6	28.8	24.6	24.9	33.0	88.6	17.5
6d	77.1	175.3	47.7	45.1	29.3	24.9	25.2	33.3	88.5	17.6
6e	76.8	175.2	47.6	44.9	29.1	24.7	25.0	33.0	88.3	17.4
7b	70.9	166.9	43.5 [d]	44.3 [d]	29.7	24.5	25.4	30.7	81.8	19.7
7d	70.8	166.7	43.2	44.2	29.7	24.5	25.4	30.7	81.2	19.5

[a] Further signals: NCH_3 (**2d**): 35.6; CH_3 (Et): 14.2 (**7b**), 14.1 (**7d**); OCH_2 (Et): 61.2 (**7b**), 61.0 (**7d**); C=O (carbamide): 151.0 (**5a**), 152.2 (**5b**); C=O (side chain, Pos 4): 173.4 (**6a**), 173.6 (**6b**), 172.6 (**6c**), 169.5 (**6d**), 168.4 (**6e**); C=O (amide): 174.9 (**7b**), 174.5 (**7d**); lines of aryl carbons, C-1': 137.8 (**5a**), 138.0 (**5b**), 135.3 (**6a**), 136.1 (**6b**), 134.4 (**6c**), 129.7 [d] (**6d**), 130.3 (**6e**), 135.3 (**7b**), 131.0 (**7d**); C-2',6': 128.0 [d] (**6a**), 120.6 (**5a,b**), 127.6 [d] (**6b**), 129.0 (**6c**), 128.2 (**7b**); C-2': 130.2 [d] (**6d**), 135.3 [d] (**6e**), 136.8 (**7d**); C-3',5': 129.0 (**5a,b**, **6c**), 128.1 [d] (**6a**), 127.8 [d] (**6b**), 127.2 (**7b**); C-3': 127.5 (**6d**), 128.2 (**6e**), 129.5 (**7d**); C-4': 124.2 (**5a,b**), 131.5 (**6a**), 131.1 (**6b**), 137.3 (**6c**), 137.7 (**6d**), 135.9 [d] (**6e**), 130.8 (**7b**), 130.5 (**7d**); C-5': 126.7 (**6d**, **7d**), 127.0 (**6e**); C-6': 129.5 (**6d**), 129.2 (**6e**), 130.0 (**7d**). [b] Measuring frequency 62.89 MHz for **4a,b** and **7a,b**. Assignments were proved by 2D-HSC (for **2a**) and DEPT measurements (for **5b** and **6a**). [c] NCH_2 (Pos 3) for **3a,b**, C=S for **4a,b**, ester C=O for **7a,b**. [d] Interchangeable assignments.

Table 5. Since the structures of **5b** and **6d** clearly substantiate the structure of **6c**, the determination of these structures will be reported elsewhere [25].

Figure 1 reveals the *N*-acyl substituent on the asymmetrically puckered seven-membered ring in the *equatorial/pseudoequatorial* position. The corresponding exocyclic torsion angles about the C3-N4 and C5-N4 bonds in **6c,d** and **5b** vary in the ranges of 159-171° and 97-104°, respectively. The O11 atoms in the endocyclic carbonyl group are equally *synperiplanar* with both neighbouring substituents (C10 and C12). The visible conformational differences can be attributed to the differences in the *N*-acyl substituents. However, the general conformation of the oxazepine rings in **5b** and **6c,d** is far from the canoni-

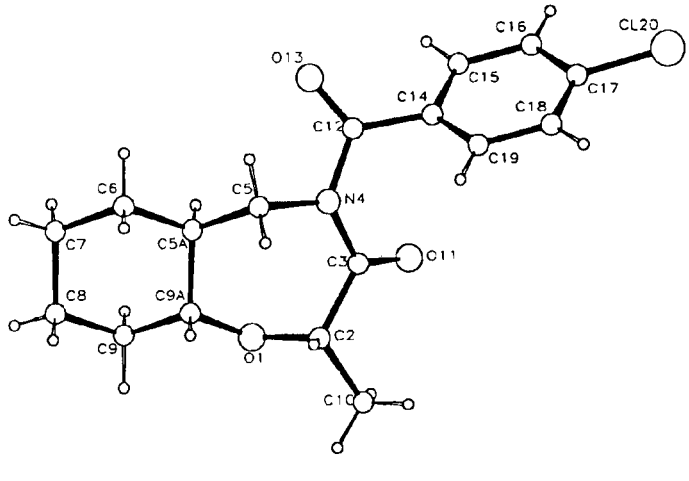


Figure 1. A perspective view of molecule **6c**. Hydrogen atoms are shown but not labelled.

Table 4

Fractional Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for **6c**. U(eq) is Defined as One-third of the Trace of the Orthogonalized Uij Tensor

Atom	x/a	y/b	z/c	U(eq)
O(1)	2466(1)	5211(1)	3116(1)	39(1)
C(2)	659(2)	5107(2)	2930(1)	39(1)
C(3)	132(2)	5794(2)	2208(1)	40(1)
N(4)	580(2)	5268(1)	1581(1)	41(1)
C(5)	1655(2)	4164(2)	1611(1)	46(1)
C(5A)	3453(2)	4304(1)	2038(1)	40(1)
C(6)	4623(3)	3315(2)	1808(1)	61(1)
C(7)	6407(3)	3359(2)	2238(1)	62(1)
C(8)	6370(2)	3342(2)	3056(1)	51(1)
C(9)	5245(2)	4353(2)	3277(1)	44(1)
C(9A)	3447(2)	4248(1)	2861(1)	36(1)
C(10)	-119(2)	5673(2)	3552(1)	52(1)
O(11)	-559(2)	6778(1)	2197(1)	60(1)
C(12)	376(2)	5915(2)	909(1)	42(1)
O(13)	1460(2)	5871(2)	511(1)	63(1)
C(14)	-1272(2)	6561(2)	680(1)	39(1)
C(15)	-1253(2)	7646(2)	303(1)	48(1)
C(16)	-2764(3)	8218(2)	27(1)	53(1)
C(17)	-4299(2)	7665(2)	113(1)	46(1)
C(18)	-4349(2)	6575(2)	472(1)	48(1)
C(19)	-2814(2)	6030(2)	763(1)	45(1)
Cl(20)	-6191(1)	8348(1)	-271(1)	70(1)

Table 5

Bond Lengths (Å) and Angles (deg.) with e.s.d.'s in Parentheses for **6c**

O1-C2	1.426(2)	C5-C5A	1.530(2)	C12-C14	1.492(2)
O1-C9A	1.433(2)	C5A-C6	1.529(3)	C14-C15	1.385(3)
C2-C3	1.534(2)	C5A-C9A	1.516(2)	C14-C19	1.381(2)
C2-C10	1.510(2)	C6-C7	1.516(3)	C15-C16	1.382(3)
C3-N4	1.383(2)	C7-C8	1.511(3)	C16-C17	1.388(3)
C3-O11	1.215(2)	C8-C9	1.518(3)	C17-C18	1.376(3)
N4-C5	1.482(2)	C9-C9A	1.520(2)	C17-Cl20	1.733(2)
N4-C12	1.416(2)	C12-O13	1.206(2)	C18-C19	1.391(2)

C2-O1-C9A	115.7(2)	C8-C9-C9A	110.6(2)
O1-C2-C3	107.8(2)	O1-C9A-C5A	112.1(2)
O1-C2-C10	106.8(2)	O1-C9A-C9	106.9(2)
C3-C2-C10	111.2(2)	C5A-C9A-C9	111.3(2)
C2-C3-N4	116.4(2)	N4-C12-013	120.5(3)
C2-C3-O11	121.4(3)	N4-C12-C14	118.2(3)
N4-C3-O11	122.1(3)	O13-C12-C14	121.1(3)
C3-N4-C5	121.9(2)	C12-C14-C15	118.8(3)
C3-N4-C12	120.4(2)	C12-C14-C19	121.0(3)
C5-N4-C12	116.1(2)	C15-C14-C19	119.7(3)
N4-C5-C5A	115.0(2)	C14-Cl5-C16	120.5(3)
C5-C5A-C6	110.0(2)	Cl5-C16-C17	118.8(3)
C5-C5A-C9A	111.8(2)	Cl6-C17-C18	121.7(3)
C6-C5A-C9A	109.6(2)	C16-C17-Cl20	118.8(2)
C5A-C6-C7	112.8(3)	C17-C18-C19	118.6(3)
C6-C7-C8	111.7(3)	C18-C17-Cl20	119.5(2)
C7-C8-C9	110.7(3)	C14-C19-C18	120.7(3)

cal forms given by Hendrickson [26] for a seven-membered ring.

EXPERIMENTAL

Melting points are not corrected. Data on the synthesized compounds are listed in Table 1. The nmr spectra were recorded in deuteriochloroform solution in 5 mm tubes at room temperature on a Bruker WM-250 (^{1}H and ^{13}C) or WP-80-SY (^{13}C) FT-spectrometers controlled by an Aspect 2000 computer at 250.13 MHz (^{1}H) and 62.89 or 20.14 MHz (^{13}C), with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were as follows: spectral width, 5 and 16 or 5 kHz; pulse width, 1.0 (^{1}H) and 7.0 or 3.5 μs (^{13}C) (~20° and ~90° flip angle, respectively); acquisition time, 1.64 and 0.40 or 1.64 s; number of scans, 16 (^{1}H) and 0.3-1 K, 25 K for **5a** and **6e** (^{13}C); computer memory, 16 K. Lorentzian exponential multiplication was applied for signal-to-noise enhancement (line width 0.7 and 1.0 or 2.0 Hz) and complete proton-noise decoupling (~0.5 or 3.5 W) for the ^{13}C-nmr spectra.

DEPT spectra [27] were run in a standard manner [28], using only the θ = 135° pulse to separate CH/CH$_3$ and CH$_2$ lines phased "up and down", respectively. Typical acquisition data were as follows: number of scans, 128-512; relaxation delay for protons, 3 s; 90° pulse widths, 17.5 and 43 μs for ^{13}C and ^{1}H, respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization. The 2D-HSC spectra [29] were obtained by using the standard Bruker pulse program "XHCORRD. AU". The number of data points was 4 K in the ^{13}C domain, and 64-256 increments were used, giving better than 5 Hz per point digital resolution in the ^{1}H domain; 256 transients were obtained with a relaxation delay of 5 s. All C-H correlations were established by using a J(C,H) value of 135 Hz to calculate the delay.

6c, Crystal data: $C_{17}H_{20}ClNO_3$ (MW = 321.8) monoclinic, space group $P2_1/c$ (No 14), a = 7.911(1), b = 11.034(1), c = 18.395(1) ß = 98.26(1)°, V = 1589.1(3) Å^3, Z = 4, D_c = 1.345 Mg.m^{-3}.F(000) = 680.

The X-ray data for the structure determination of **6c** were collected on an Enraf Nonius CAD-4 diffractometer equipped with a graphite monochromator, using MoK_α radiation (λ = 0.71070 Å).

A crystal with dimensions of 0.50 x 0.45 x 0.35 mm was applied. The cell dimensions were obtained by means of a least squares procedure from the setting angles of 25 carefully centered reflections. The intensities of all reflections within the interval 2 < 2θ < 33° were measured in the ω -2θ mode at 293 K. After conventional data reduction (with μ = 0.25 mm^{-1}, no absorption correction was applied), 6007 of 6530 reflections were unique and not systematically absent. The intensities of three standard reflections measured every hour remained constant within experimental error throughout data collection.

The structure was solved by direct methods (SHELXS-86) [30]. The structure was refined on F^2 values by the program SHELXL-93 [31] for 201 parameters, which resulted in the final residuals R1[I > 2σ(I)] = 0.047 and wR2 = 0.142 (R_{tot} = 0.083), S = 1.064. The highest peaks in the final difference map were 0.165 and -0.133 eÅ^3, while the greatest shift-over error was 0.001. The H atoms were generated from assumed geometries and were refined in riding mode with the adjacent heavy atoms. The calculations were carried out on a DEC-5000 computer. Scattering factors were taken from tables [32].

trans-2-Aminomethylcyclohexanol **1a** and *trans*-2-methylaminomethylcyclohexanol **1b** were prepared by literature methods [33].

trans-2-Phenoxyacetylaminomethylcyclohexanol.

To a mixture of 6.15 g (0.05 mole) of *trans*-2-aminomethylcyclohexanol in 60 ml of dry benzene and dried potassium carbonate, 9.28 g (0.055 mole) of phenoxyacetyl chloride was added dropwise with stirring. The benzene solution was shaken in turn with water, dilute hydrochloric acid and water, dried (sodium sulfate) and evaporated to dryness. The residue was recrystallized from an ether-petroleum ether mixture, mp 84-86°, yield 81%.

Anal. Calcd. for $C_{15}H_{21}NO_3$ (263.34): C, 68.42; H, 8.04; N, 5.32. Found: C, 68.27; H, 7.86; N, 5.19.

trans-2-Phenoxyethylaminomethylcyclohexanol **1c**.

Two g (0.0076 mole) of *trans*-2-phenoxyacetaminomethylcyclohexanol was reduced in a mixture of 1.0 g (0.026 mole) of LAH dissolved in 80 ml of ether with stirring and refluxing for 10 hours. After decomposition of the excess of LAH with water (2 ml), the mixture was dried (sodium sulfate), filtered and evaporated. The residue, a colorless oil, was transformed to the hydrochloride, which was recrystallized from ethanol-ether, mp 119-121°, yield 92%.

Anal. Calcd. for $C_{15}H_{24}ClNO_2$ (285.82): C, 63.04; H, 8.46; N, 4.90; Cl, 12.40. Found: C, 62.87; H, 8.53; N, 4.69; Cl, 12.21.

trans-Perhydro-1,4-benzoxazepin-3-ones **2a-e**.

To a suspension of 0.55 g (0.011 mole) of sodium hydride

(50% in oily dispersion) in 40 ml of absolute benzene, 1.23 g (0.01 mole) of *trans*-2-aminomethylcyclohexanol dissolved in 10 ml of benzene was added dropwise and the mixture was stirred for 15 minutes at room temperature. After the cessation of hydrogen formation, the mixture was cooled and 0.01 mole of ethyl chloroacetate (or ethyl 2-chloropropionate) was added dropwise to the mixture. After stirring for 60 minutes and refluxing for 90 minutes, the cooled mixture was shaken with 3 x 15 ml of hydrochloric acid (5%), followed by 2 x 15 ml of cold water. The separated benzene layer was dried (sodium sulfate) and evaporated under reduced pressure. The product was purified by recrystallization or by distillation under reduced pressure.

trans-Perhydro-1,4-benzoxazepines **3a,b**.

To a water-free ether suspension of a 6-fold amount of LAH (1.12 g in 70 ml of ether), 0.01 mole of 1,4-oxazepin-3-one derivative was added and the mixture was stirred under reflux for 18 hours. The excess of LAH was carefully decomposed by the addition of water (2 ml) and the mixture was dried (sodium sulfate). The separated ether solution was evaporated and the residue was distilled under reduced pressure. The bases were transformed to the hydrochloride or picrate and purified by recrystallization from ethanol.

trans-Perhydro-1,4-benzoxazepine-3-thiones **4a,b**.

The appropriate *trans*-perhydro-1,4-benzoxazepin-3-ones (0.01 mole) was heated with 4.0 g of phosphorus(V)sulphide in 30 ml of pyridine at 70-80° for 5 hours. During standing overnight, the product solidified. The mixture was poured into a mixture of 100 g of ice and 15 ml of concentrated hydrochloric acid. The resulting crystals were separated and recrystallized from dilute ethanol (70%).

trans-4-Phenylaminocarbonylperhydro-1,4-benzoxazepin-3-ones **5a,b**.

Compound **2a** or **2b** (0.01 mole) in 15 ml of water-free benzene was refluxed with 1.31 g (0.011 mole) of phenyl isocyanate for 60 minutes. The reaction was monitored by tlc. The solvent was evaporated off under reduced pressure and the oily residue was crystallized. The product was recrystallized from ether.

trans-4-Aroylperhydro-1,4-benzoxazepin-3-ones **6a-e**.

Compound **2** (0.01 mole) was dissolved in 15 ml of pyridine and the mixture was shaken with 0.011 mole of the aroyl chloride at room temperature for 2 hours. The acylation was monitored by tlc. The reaction mixture was poured into ice-water acidified with concentrated hydrochloric acid and extracted with 3 x 15 ml of ethyl acetate. After drying (sodium sulfate), the organic solvent was evaporated off under reduced pressure. The oily residue was crystallized from dilute ethanol (70%).

trans-2-(1-Carbethoxyethoxy)-1-aroylaminomethylcyclohexanes **7b,d**.

Compound **6b** or **6d** (0.5 g) was dissolved in hot ethanol (15 ml), 6 drops of ethanol saturated with hydrochloric acid was added and the mixture was allowed to stand overnight at room temperature. The reaction was monitored by tlc. The product was separated on a preparative layer (20 x 20 cm x 0.25 mm silica gel activated at 105° for 60 minutes; solvent: benzene-methanol 18:2).

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