Tetrahedron Vol. 43, No. 19, pp. 4359 to 4366, 1987
Printed in Great Britain.

0040-4020/87 $3.00 + .00

STEREOCHEMICAL STUDIES, 105. SATURATED HETEROCYCLES, 109[1]

SYNTHESIS AND STERIC STRUCTURES OF PERHYDRO-4,1-BENZOXAZEPIN-2-ONES

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(*Received in UK* 30 *July* 1987)

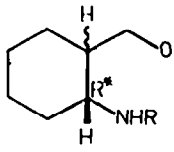
Abstract - cis- and trans-2-Hydroxymethylcyclohexanol were cyclized with ethyl chloroacetate or ethyl 2-chloropropionate in the presence of sodium hydride to synthesize stereoisomeric perhydro-4,1-benzoxazepin-2-ones (4-9). The relative configurations and predominant conformation of the compounds prepared were confirmed by ^{1}H and ^{13}C NMR spectroscopy.

We earlier studied the synthesis and steric structures of perhydro-1,3- and 3,1-benzoxazine derivatives[2-4] synthesized by the ring closure of 1,2-disubstituted 1,3-difunctional alicyclic compounds, e.g. aminoalcohols 1-3. In the present paper we report the synthesis and chemical and spectroscopic investigation of some related cyclohexane-fused seven-membered 1,4-heterocycles. This work was prompted by pharmacological considerations too, because some of the analogous saturated heterocycles possessed favourable biological activity,[5] and pharmacological study of the saturated analogues of benzodiazepine-like[6] structures seemed to be promising.

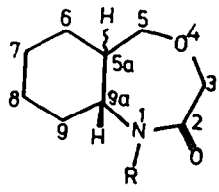
Synthesis

α-Haloacetic acid derivatives, generally used C-C fragments[7] for the synthesis of 1,4-oxazepin-3-ones and aminoalcohols 1-3, were applied as starting materials. Compounds 1-3 with ethyl chloroacetate in the presence of NaH afforded perhydro-4,1-benzoxazepin-2-ones 4-6 in 20-56% yields. With ethyl bromoacetate, used for the synthesis of the aromatic analogue 1,4-benzoxazepin-2-ones,[8] much lower yields were attained. All compounds investigated were racemates. The diagrams show only the enantiomer in which the configuration of the C-1 atom of the starting molecules 1-3 is R.

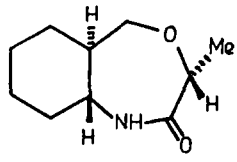
The reaction of 2 with ethyl 2-chloropropionate gave a mixture of diastereomers 7 and 8, from which 7 was separated by fractional crystallization. Preparation of the pure isomer 8 failed; only an enrichment of 8 could be achieved. The reaction of ethyl 2-chloropropionate with cis-aminoalcohol 1 resulted in the formation of compound 9 after column chromatographic purification. The ring closure reactions employed for the preparation of 1,4-oxazines[9,10] in good yield could not be applied successfully for the present compounds. Interestingly, from 10 in methanol in the presence of KOH, the methyl ether 11 was formed in good yield instead of the expected 5.



cis, R = H: 1
trans, R = H: 2
cis, R = Me: 3



cis, R = H: 4
trans, R = H: 5
cis, R = Me: 6



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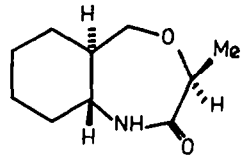

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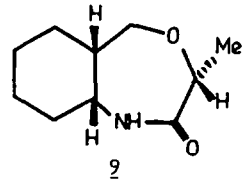

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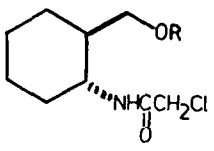
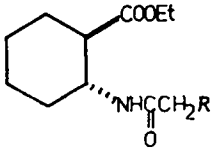
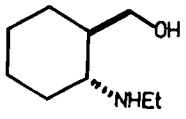
The ^{1}H and ^{13}C NMR data supporting the structure 11 are the O-methyl singlet of 3H intensity at 3.43 ppm, and the characteristically downfield shifted[11a] methoxy carbon signal at 59.2 ppm. The latter assignment to a primary carbon atom was proved by DEPT measurement.[12,13] The presence of the lactam moiety is unambiguously shown by the νNH and amide-I IR bands (3380 and 1639 cm^{-1}) and the carbonyl line at 170.3 ppm in the ^{13}C NMR spectrum. Futhermore, the ^{1}H and ^{13}C NMR signals of the chloro and O-methylene groups (3.88, 3.95 ppm, 2xd, and 3.35, 3.65 ppm, 2xdd; 63.7 and 71.8 ppm, respectively), those of the NCH group (^{1}H: 3.75 m; ^{13}C: 48.6 ppm), and those of the further nine cyclohexyl protons (1.1-2.0 ppm, partially overlapping multiplets of 9H intensity) and the corresponding five carbon lines (25.5, 25.7, 28.8, 33.2 and 46.8 ppm) could be identified.



R = H: 10
R = Me: 11



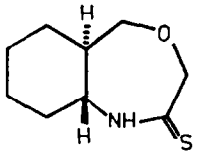
R = Cl: 12
R = H: 14



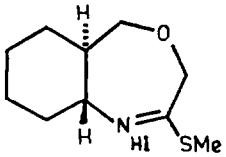
13

$LiAlH_4$ reduction of the N-chloroacetyl derivative 12 of ethyl trans-2-aminocyclohexanecarboxylate similarly failed to afford the desired oxazepine 17. Here only N-ethyl-trans-2-hydroxymethylcyclohexylamine (13) was formed. For verification of the structure of 13, it was also synthesized from 14, in an authentic way.

On reaction with P_4S_{10} in pyridine, 5 gave the 2-thioxo compound 15, which with methyl iodide afforded the thioether 16, from which 5 could be recovered by mild alkaline treatment. $LiAlH_4$ reduction of 5 yielded trans-4,1-perhydrobenzoxazine 17.



15



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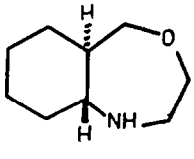


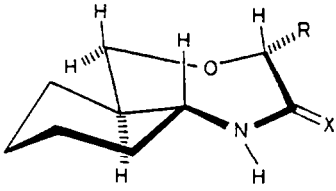
17

Some further usual reactions of lactams,[14,15] however, could not be carried out. For example, after the refluxing of 5 in an excess of acetic anhydride for 2 h, or after a 3 h refluxing of 2 in toluene with phenyl or methyl isocyanate, the unreacted starting material was recovered.

Conformational studies

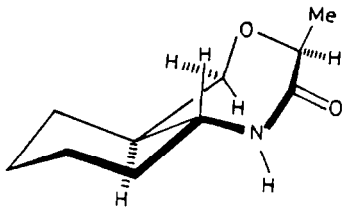
The spectroscopic data supporting the structures of the oxazepine derivatives are given in Tables 1 and 2. In the trans compounds, the connection of the hetero ring to the cyclohexane ring with the chair conformation is, of course, diequatorial. The flexibility of the seven-membered hetero ring renders feasible

several relatively stable conformations. Consequently, the conformations postulated below are the most probable on the basis of the NMR data, though in some cases they are not proved unambiguously. Nevertheless, in each of the cis and trans series two conformations (A-D) with high probability can be selected by taking into account[16] the coupling constants J(5'ax,5a) and J(5eq,5a) and the Dreiding model investigations, excluding sterically unfavourable conformations.



X = O, R = H: 5
X = O, R = Me: 7
X = S, R = H: 15

A



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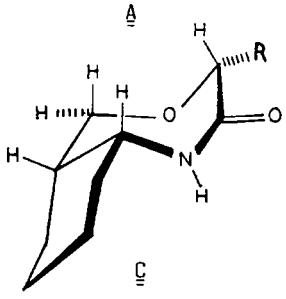
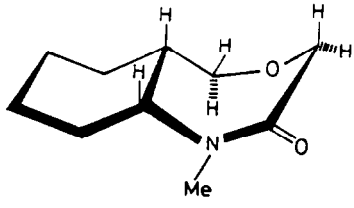
B



R = H: 4
R = Me: 9

C



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D

For determination of the preferred conformations, comparison of the H-9a signals of the cis-trans isomer pairs is decisive. The H-9a signal in the spectra of the trans isomer 5 and the N-methyl cis isomer 6 is upfield shifted by more than 0.8 ppm, and is wider by 10 Hz compared with that of the cis compound 4. Consequently, H-9a, which is certainly axial in 5, must be axial in 6 as well. In the cis isomer 4, however, it should be equatorial relative to the cyclohexane ring. Thus, in accordance with our earlier results[17-19] for tetramethylene-1,3-heterocycles, in the dominant conformation of the N-unsubstituted compund 4, the 5-methylene group is attached equatorial, while the NH group is axial to the cyclohexane ring, whereas in the case of 6 the situation is reversed: the bulky N-methyl group is equatorial and the 5-methylene group is axial.

Since the values of the vicinal coupling J(5eq,5a) and J(5'ax,5a), are considerably different in the trans isomer 5 (4.7 and 8.9 Hz, respectively) and one of them is relatively large, one of the dihedral angles must be ~180°, whereas the other one is expected[16] to be near to 60°. These conditions are met for 5 by form A. In conformation A with a chair-like hetero ring, the amide moiety (the C-2 and N-1 atoms) is located on one side of the plane determined by the O-4 and C-3, 5a,9a atoms, while the C-5 atom is situated on the other side.

The C(5a)-H,C(5')-H(ax) and C(5a)-H,C(5)-H(eq) dihedral angles in the cis N-methyl derivative 6 are similar to those in 5 (the corresponding coupling constants are 11.0 and 6.2 Hz, respectively), and therefore analogous conformations with an equatorial N-methyl group should be considered. If a distorted boat form of the alicycle is assumed, the molecule can avoid all steric hindrances, and simultaneously all the conditions revealed by the spectra data the equatorial position of the NMe group and ~180° dihedral angle of the C(5a)-H and C(5')-H(ax) bonds are satisfied. Thus, a flexible form close to B can be postulated.

In the case of the cis isomer 4, the chair-like form of the hetero ring is the preferred one, to which the C-6 atom is linked axially (C). In this structure the H-5a,H-5'(ax) and H-5a,H-5(eq) dihedral angles are around 60°, in agreement with the nearly equal and small values of the coupling constants (one is 3.0 Hz, while

the other is also lower than 5 Hz, but could not be determined exactly because of the signal overlaps.

Table 1. IR (KBr, cm^{-1}) and ^1H NMR data (δ_{TMS} = 0 ppm, coupling constants, Hz) in $CDCl_3$ at 250 MHz on compounds 4-9, 15 and 17

Compound	νNH band	amide-I band	δNH band	H-3 2xd/qa (2/1H)[a]	H-5 2xdd (2x1H)[b]		H-5a,6,7,8,9 m's (9H)	H-9a m (1H)	NH ~s(1H)[c]
4	3320	1655	1540	3.9[d]	3.56	3.93[d]	1.2-1.8, 2.22[e]	4.10	7.57
5	3219	1657	1433	4.12, 4.21[f]	3.33[d]	3.97	0.85-2.05	~3.3[d,g]	~6.5
6	-	1640	-	~4.2	3.76	3.93	1.3-1.95, 2.55[e]	3.20	3.00
7[h]	3194			3.98	3.35	4.05	0.8-2.1	3.17	5.75
8[h]	3076	1657	1447	4.20	3.60[d]	3.83	1.1-2.2	~3.6[d,g]	~6.6
9[h]	3215	1660	1450	4.04	3.81	3.92[d]	1.25-1.9	3.96[d]	5.57
15	3202	-	1541	4.38, 4.71[f]	3.38	3.99	0.8-2.2	3.50	~8.3
17	~3300	-	1450	~3.8[d]	~3.4	~3.8[d]	0.8-1.9	2.25	

[a] AB type multiplet, J(A,B): 15.2 (5) and 15.6 (15), for 4 and 6 near to the A_2 ($\delta A \cong \delta B$) limiting case, s (2H); or quartet (A part of an AX_3 spin system) for 7, 8 and 9. The H-2,3 protons of 17 consist of an AA'BB' spin system: H-2: 2.9-3.2 m (2H). [b] AB part of an ABX spin system (B stands for the more shielded methylene proton). Values of J(A,B), J(A,X) and J(B,X): 9.6, ? and 3.0 (4), 12.4, 4.7 and 8.9 (5), 12.2, 6.2 and 11.0 (6), 12.5, 4.0 and 10.4 (7), 12.7, 3.0 and 6.8 (8), 12.5, 2.8 and 3.2 (9), 12.4, 4.8 and 9.2 (15), ~13, ? and ~10 (17). [c] Broad signal, for 6 s (3H) of NCH_3 group. [d] Overlapping signals. [e] H-5a, m (1H). [f] Further doublet splitting by 1.2 (5) and 0.9 (15), due probably to H-3(e),NH coupling. [g] Half band-width for 5 and 8 is smaller (~20 Hz) than for 4 and 7 (~30 Hz), respectively. [h] CH_3(Pos. 3), d (3H) and J(CH_3,H-3): 1.34 and 6.6 (7), 1.47 and 6.9 (8), 1.36 and 6.5 (9).

The structures 4 (C) and 6 (D) are also supported by the ^{13}C NMR data. If the data on 4 and 6 are compared with to those on *trans* isomer 5, the majority of the carbon atoms are observed to be more shielded due to the field effect[20] (steric compression shift). Analogously to the observations on *cis* and *trans* decalins,[21] this field effect can be anticipated mainly for the signals of the bridgehead carbons C-5a and C-9a, and apart from the C-9a atom in 6 - where the α-effect of the methyl substituent[22] overcompensates - it can be observed: the field effects for the C-9a (4) and C-5a (4, 6) atoms are 4.2, 6.6 and 6.6 ppm, respectively.

As a proof of conformation C, field effects were observed in the spectrum of 4 for the C-6, C-8 and C-9 signals as well (3.7, 3.0 and 4.6 ppm, respectively), whereas the C-7 line was shifted in the opposite direction by 3.5 ppm. Considerable field effects were found for the C-2, C-3 and C-5 atoms too (7.5, 2.0 and 5.0 ppm, respectively). Conformation D for 6 is supported by the field effects observed on the C-3, C-5, C-6 and C-9 signals (4.0, 5.5, 8.2 and 4.2 ppm, respectively).

The *trans* annelation of the isomeric pair 7 and 8 comes from the synthetic pathway; the only difference is in the configuration of C-3. The spectral data support an analogous conformation (A) with *equatorial* C-3 methyl group for 7, as in the case of 5.

For 8, this conformation would lead to a very unfavourable 1,3-*diaxial* interaction between the 3-methyl group and the H-9a or H-5'(*ax*) atom. All the ^{13}C

Table 2. ^{13}C NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds 4-9, 15 and 17 in $CDCl_3$ solution at 62.9 or 20.1 MHz[a]

Compound	C-2	C-3	C-5	C-5a	C-6	C-7	C-8	C-9	C-9a	CH_3
4	167.0	71.2[b]	72.8[b]	37.4	24.0	27.7[c]	21.4	27.7[c]	50.0	-
5	174.5	73.2	77.8	44.0	27.7	24.2[b]	24.4[b]	32.3	54.2	-
6	171.9	69.2	72.3	37.4	19.5	25.5[b]	25.7[b]	28.1	63.5	35.4
7[d]	175.4	76.5	79.2	43.6	27.0	24.5[b]	24.9[b]	32.9	55.2	16.9
8	176.1	72.5	79.7	45.7	32.3	25.2[b]	24.7[b]	30.7	51.9	18.8
9	175.3	76.8[b]	76.9[b]	41.3	24.0	31.7	19.6	25.6	50.3	16.9
15	205.5	79.3	78.1	43.1	27.9	24.3[b]	24.4[b]	32.6	59.6	-
17[d]	63.6	71.5	75.2	48.6[b]	35.0	25.8[e]	25.6[e]	29.2	49.0[b]	-

[a] Measuring frequency 62.9 MHz for 4, 15 and 17. [b,e] Reversed assignments may also be possible. [c] Two overlapping lines. [d] Assignments were proved by DEPT measurements.

chemical shifts of 7 are identical within 1.4 ppm to those of the analogues 5, except that of C-3 (which is downfield shifted by 3.3 ppm) due to its methyl substitution. In accordance, all NMR data on isomer 8 are characteristically different. The H-9a signal is downfield shifted (though it does not reach the value for the corresponding equatorial hydrogen of the cis isomer 4), its half band-width is less, and both vicinal coupling constants J(5a,5'ax) and J(5a,5eq) are smaller.

In the dominant conformer of 8, a twist-boat hetero ring is annelated to the cyclohexane ring with chair conformation (B), in which the two dihedral angles are about 20° and 100°, respectively, and the 3-methyl group is quasiaxial. The deshielding of H-9a relative to that in 5 and 7 can be explained by the anisotropic effect[13b] of the near O-4 atom. Conformation B for 8 is also supported by the ^{13}C NMR data. The shift differences relative to those measured for 7 are within 0.7 ppm for atoms C-2,5,7,8,9. Field effects of 4.0 and 3.3 ppm were observed for the C-3 and C-9a lines, due to the O-4,H-9a steric interaction. The downfield shifts of the C-5a and C-6 lines (by 2.1 and 3.3 ppm) are due to the absence of steric hindrance between the diaxial H-5' and H-6' atoms in 7.

In agreement with the above, in the cis isomer 9 the downfield shift of the H-9a signal is even higher, and is nearly as high as that in 4. Hence, the NH group is axial as in 4. Since the H-5a,H-5'(ax) and H-5a,H-5(eq) couplings are similarly small, conformation C is preferred, involving the (r-9a,c-3,c-5a) configuration.

If conformation C is assumed for the r-9a,t-3,c-5a isomer, strong steric interactions would be present between the methyl group and the H-9a and H-5'(ax) atoms, but no sign of this can be detected in the NMR spectra. Furthermore, as a consequence of the analogous steric structures, the ^{13}C NMR shifts for 4 and 9 are very similar to each other. The chemical shifts of C-2 and C-3 are of course much higher, due to the α and β-effects[11c,22] of the methyl substituent.

Since the NMR data on 15 are completely analogous to those on 5, the similar structure and hence the preference for conformer A are obvious. A characteristically large downfield shift can be observed for the C-2 line, which unambiguously shows the presence of the thiocarbonyl group.[13] This also explains the shifts of the C-3 and C-9a lines in the same direction, though to a lesser extent.

The structure of 17, obtained by reduction of the carbonyl group to methylene, is unambiguously proved by the spectra. The amide-I band is absent from the

IR spectrum; in the ^{1}H NMR spectrum the AB multiplet of the 2-methylene group of 2H intensity is replaced by the AA'BB' multiplet of the NCH_2CH_2O moiety of 4H intensity; in the ^{13}C NMR spectrum, instead of the carbonyl signal at around 170 ppm, the C-2 line appears at 63.6 ppm. Due to signal overlap in the ^{1}H NMR spectrum and partly to the higher flexibility of the fully saturated hetero ring, no information can be obtained about the conformation from the routine measurements.

The hypothetical conformation A of 5 was confirmed by differential nuclear Overhauser (DNOE) experiments. On saturating the doublet (at 4.12 ppm) of H-3'(ax), we observed intensity enhancements for the H-5'(ax) and H-9a signals. These hydrogens are in the 1,3-diaxial position, and hence in steric proximity with H-3'(ax) in structure A. Similarly, on saturation of the H-5'(ax) and H-9a signals of 7 with an analogous postulated conformation (A) in the DNOE measurement, the intensity of the H-3'(ax) quartet exhibited a significantly higher intensity, proving their 1,3-diaxial position and also the equatorial and trans arrangement of the 3-methyl group relative to the H-5'(ax) and H-9a atoms.

Acknowledgements

Thanks are due to Mr. I. Pelczer for measuring the DNOE spectra. We are indebted to Mrs. J. Csákvári, Mrs. É. Mogyorósi, Miss M. Sípos and Mr. A. Fürjes for skilled technical assistance.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ solution in 5 and 10 mm tubes, on Bruker WM-250 (^{1}H, ^{13}C) and WP-80 SY (^{13}C) FT spectrometers controlled by ASPECT 2000 computer at 250.13 (^{1}H) and 63.89 or 20.14 MHz (^{13}C), respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: sweep width 5 kHz, pulse width 1 (^{1}H) and 7 or 3.5 (^{13}C) us (~20 and ~30 flip angle), acquisition time 1.64 and 1.02 or 1.64 s, number of scans: 16 or 32 (^{1}H) and 1 K-4 K (^{13}C), computer memory 16 K. Complete proton noise decoupling (~3 or 1.5 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).

DEPT[42] spectra were run in a standard way,[43] using only the $\theta = 135^\circ$ pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively. Typical acquisition data were: number of scans 128-12 K, relaxation delay for protons 3 s, 90° pulse widths 10.8 and 22.8 μs for ^{13}C and ^{1}H, respectively. The estimated value for J(C,H) resulted in 3.7 ms delay for polarization. Gated decoupling to generate NOE was used with a selective preirradiation time of 3-5 s and a decoupling power (CW mode) of ca. 30-40 mW; number of scans 64-256, dummy scans 4-8, pulse width 4.7 μs (90°), 8 K data points for ca. 2000 Hz sweep width. Line broadening of 1.0-2.0 Hz was applied to diminish residual dispersion signals in the difference spectra.

General procedure for the preparation of condensed 1,4-oxazepin-2-ones (4-9)

To a solution of 10 mmol aminoalcohol in 20 ml dry benzene, 10 mmol ethyl chloroacetate or ethyl 2-chloropropionate and 12 mmol NaH (80% oily dispersion) were added at room temperature under stirring. The reaction mixture was stirred for 10 min at ambient temperature, then refluxed for 1 h during stirring. After cooling to room temperature, 50 ml benzene was added. Washing followed with 30 ml 5% ice-cold HCl and 30 ml water. After drying (Na_2SO_4), the benzene phase was evaporated to give 5 in crystalline form. In the cases of 4, 6 and 9, the pale-yellow oil obtained after the evaporation was purified by column chromatography on 50 g aluminium oxide of activity 2, with benzene as eluent.

The crude products obtained in the preparation of 7 and 8 were crystallized from ethyl acetate, and the diastereomer 7 was obtained in pure form. On crystallization of the crude product from n-hexane, a 2:5 mixture of 7 and 8 was obtained (m.p. 159-177 °C).

Attempted alkaline ring closure of 10

5 ml of 10 (m.p. 100-103 °C, di-isopropyl ether), obtained from 2 with $ClCH_2COCl$, was stirred for 7 h in MeOH (20 ml) containing 1 g KOH. After evaporation of the reaction mixture, the residue was dissolved in 20 ml cold water, neutralized with HCl and extracted with 3x30 ml $CHCl_3$. After evaporation of the $CHCl_3$ extract, a crystalline product was obtained, which was proved by ^{1}H and ^{13}C

NMR investigations to be 11. Yield 71%. M.p. 81-83 °C (n-hexane). Anal. for $C_{10}H_{18}ClNO_2$ (219.71), calcd/found: C, 54.66/54,61; H, 8.26/8.41; N, 6.38/6.41.

Table 3. Analytical data on compounds 4-9 and 15-17

Compound	Yield (%)	M.p. (°C)	Found (%) C	H	N	Formula (M.w.)	Calculated (%) C	H	N
4	20	210-211[a]	63.71	8.99	8.33	$C_9H_{15}NO_2$ (169.22)	63.88	8.94	8.33
5	56	157-158[b]	63.79	9.03	8.19	$C_9H_{15}NO_2$ (169.22)	63.88	8.94	8.28
6	25	oil	65.44	9.61	7.50	$C_{10}H_{17}NO_2$ (183.25)	65.55	9.35	7.64
7	29	180-184[a]	65.55	9.52	7.74	$C_{10}H_{17}NO_2$ (183.25)	65.55	9.35	7.64
9	40	152-154[b]	65.41	9.50	7.56	$C_{10}H_{17}NO_2$ (183.25)	65.55	9.35	7.64
15	64	124-126[b]	58.38	8.21	7.70	$C_9H_{15}NO_5$ (185.28)	58.34	8.16	7.56
16	79	136-140[c]	36.82	5.64	4.33	$C_{10}H_{18}INOS$ (327.22)	36.70	5.54	4.28
17	84	227-231[c]	56.19	9.50	7.47	$C_9H_{18}ClNO$ (191.70)	56.38	9.46	7.31

[a] Ethyl acetate. [b] Di-isopropyl ether. [c] Ethanol/ether.

Attempted reductive ring closure of 12

To a stirred suspension of 1 g $LiAlH_4$ in 50 ml dry THF, 5 mmol (1.24 g) acyl derivative 12, obtained by acylation of ethyl trans-2-aminocyclohexanecarboxylate with $ClCH_2COCl$ (m.p. 84-86 °C, n-hexane), was added. After a 1 h reflux, the reaction mixture was worked up as usual. The oily product was converted to the HCl salt with ethanolic HCl, and was proved by elemental analysis to be compound 13.

13 was also synthesized in an authentic way. $LiAlH_4$ reduction of 14 obtained by acetylation of trans-2-aminocyclohexanecarboxylic acid yielded 13, which was identical with that obtained from 12.

2-Thioxo-trans-perhydro-1,4-benzoxazepine (15)

0.5 g 5 and 1 g P_4S_{10} in 20 ml pyridine was refluxed for 1 h under stirring. The reaction mixture was poured onto ice and allowed to stand overnight, and the precipitated 15 was filtered off and washed with water. $CHCl_3$ extraction of the mother liquor yielded an additional amount of 15.

Reaction of 15 with methyl iodide

0.5 g 15 was allowed to stand for one day at room temperature with 1 ml MeI in 25 ml acetone. Evaporation of the reaction mixture yielded a brown oily product (16), which gave a crystalline product on trituration with ether.

Reduction of 5 with $LiAlH_4$

10 mmol (0.30 g) $LiAlH_4$ was suspended in 50 ml dry THF and stirred for 10 min, after which 5 (5 mmol, 0.85 g) was added. After a 1 h reflux, the reaction mixture was evaporated, and the resulting oil was converted to the HCl salt for the analysis. For the spectroscopic investigations, the base liberated from the HCl salt was used.

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