Tetrahedron Vol. 41, No. 7, pp. 1353 to 1365, 1985
Printed in Great Britain.

0040-4020/85 $3.00+.00

STEREOCHEMICAL STUDIES 83[1]
SATURATED HETEROCYCLES 76[1]

PREPARATION AND CONFORMATIONAL STUDY OF PARTIALLY SATURATED 3,1-BENZOXAZINES, 3,1-BENZOXAZIN-2-ONES AND 3,1-BENZOXAZINE-2-THIONES

GÁBOR BERNÁTH*, GÉZA STÁJER, ANGELA E. SZABÓ, FERENC FÜLÖP

Institute of Pharmaceutical Chemistry, University Medical School, Szeged, POB 121, H-6701 Szeged, Hungary

and

PÁL SOHÁR

Spectroscopic Department, EGYT Pharmaceutical Works, POB 100, H-1475 Budapest, Hungary

(*Received in UK 2 January* 1985)

Abstract - The cis- and trans-2-amino-4-cyclohexene-1-carboxylic acids 1 and 3 react with imidates to give the condensed-skeleton, bicyclic cis- and trans-pyrimidin-4-ones 8 and 9. The amino acids 1 and 3 were reduced to the cis- and trans-1,3-aminoalcohols 6 and 7, which were cyclized by means of imidates to the bicyclic tetrahydro-4H-3,1-benzoxazines 10 and 11, or were converted, via the corresponding carbamates 14 and 15 into the tetrahydro-4H-3,1-benzoxazin-2(1H)-ones 16 and 17. The 2-thioxo analogues 18 and 19 were prepared by cyclization of the dithiocarbamates obtained from the aminoalcohols 6 and 7 by treatment with carbon disulphide. The trans-aminoalcohol 7 and its saturated analogue reacted with p-chlorobenzaldehyde to furnish the hexahydro 13 and octahydro-4H-3,1-benzoxazine 13a, respectively. ^1H and ^{13}C NMR studies showed that, similarly to the earlier-investigated analogues containing oxygen or unsubstituted nitrogen at position 1, the synthesized cis isomers 8, 10, 16 and 18 occurred as the preferred conformer in the heterocyclic twist inverse form of N-inside type (quasiaxial C_6-N bond) (B). In the trans isomers containing a saturated C-2 atom (13 and 13a), H-2 and H-6 are in cis relative positions.

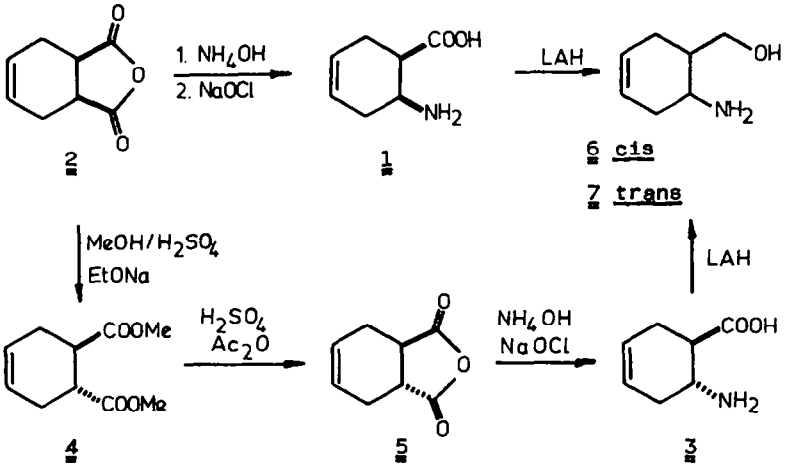
In earlier papers we reported the conversions of cis- and trans-2-(aminomethyl)-1-cyclohexanol, cis- and trans-2-(hydroxymethyl)-1-cyclohexylamine, and their homologues containing cyclopentane, cycloheptane and cyclooctane skeletons, to fused-skeleton dihydro-[2] and tetrahydro-1,3-oxazines[3], 1,3-oxazin-2-ones and 1,3-oxazine-2-thiones[4-6], and also the oxazine derivatives isomeric as concerns the relative positions of the heteroatoms[2-6]; further, 1,3-oxazin-4-ones[7] were prepared from alicyclic cis- and trans-2-hydroxy-1-carboxamides. ^1H NMR investigations showed that the O-inside conformer was predominant in the cis-5,6-tetramethylene-1,3-oxazin-2-ones obtained from 2-(aminomethyl)-1-cyclohexanols; in contrast, the N-inside conformer[3,8] was preferred in cis-4,5-

tetramethylene-1,3-oxazine and analogues with unsubstituted nitrogen which were prepared from 2-(hydroxymethyl)-1-cyclohexylamine, whereas the N-substituted derivatives of cis-1,3-oxazine and cis-1,3-oxazin-2-one had the N-*outside* conformer as the favoured form[9]. The predominant conformations determined in solution were confirmed in many cases by X-ray diffraction analysis (see, e.g.[10,11]).

The present work is concerned with the synthesis of fused-skeleton, bicyclic, partially saturated 3,1-benzoxazines, 3,1-benzoxazin-2-ones and 3,1-benzoxazine-2-thiones containing an unsaturated carbocycle, and with the preparation of the related pyrimidinones. Systematic ^{1}H and ^{13}C NMR studies and X-ray diffraction analyses were used to compare the conformations of the tetramethylene-1,3-heterocycles studied in detail earlier, and of the unsaturated analogues reported in the present paper.

Other objects of the present research are the synthesis of biologically active compounds and study of the structure-activity relationship. Our earlier investigations showed the cis-trimethylene-condensed 1,3-heterocycles to be more pharmacologically active than the corresponding tetramethylene-condensed analogues[12]. This suggested the possible greater biological activity of the compounds in this series containing the cyclohexene structural unit, since this ring ensures better coplanarity of the molecule than in the cyclohexane analogues. It is a special advantage that the starting material of the title compounds is the readily available cis-1,2,3,6-tetrahydrophthalic anhydride, and the reactive double bond in the heterocyclic products affords wide possibilities for further reactions.

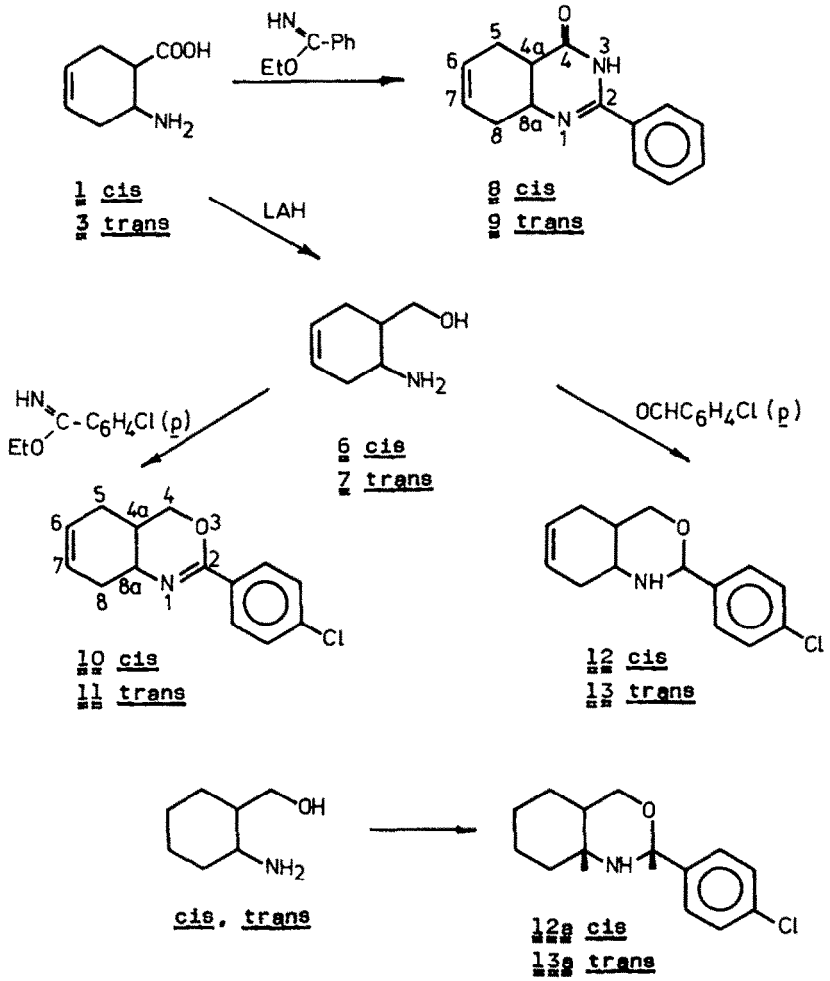
The starting cis-2-amino-4-cyclohexene-1-carboxylic acid **1** was prepared by Hofmann degradation of the carboxamide obtained by ammonolysis of cis-1,2,3,6-tetrahydrophthalic anhydride **2** (Scheme 1). The Hofmann reaction was effected with hypochlorite[14], in contrast with our earlier hypobromite method for preparing cis-2-amino-1-cyclohexanecarboxylic acid[13]. The trans-amino acid **3** was also prepared from **2**; methanolysis of the anhydride **2** gave dimethyl cis-1,2,3,6-tetrahydrophthalate, which was epimerized with sodium ethoxide (analogously to the reaction of dimethyl cis-hexahydrophthalate[15]) to yield the trans isomer **4**. Subsequent hydrolysis gave trans-1,2,3,6-tetrahydrophthalic acid, which was converted to the trans-dicarboxylic acid anhydride **5**. Ammonolysis of the latter and degradation of the monoamide with sodium hypochlorite yielded the trans-amino acid **3**. Lithium aluminium hydride reduction of the amino acids **1** and **3** furnished the cis- and trans-aminoalcohols **6** and **7**.



2 **1** **6** cis **7** trans **4** **5** **3**

Scheme 1

The amino acids 1 and 3 react with ethyl benzimidate to yield the cis- and trans-2-phenyl-4a,5,8,8a-tetrahydroquinazolin-4(3H)-ones 8 and 9 (Scheme 2). Reaction of the aminoalcohols 6 and 7 with ethyl p-chlorobenzimidate gives the cis- and trans-2-(p-chlorophenyl)-4a,5,8,8a-tetrahydro-4H-3,1-benzoxazines 10 and 11; with p-chlorobenzaldehyde the cis- and trans-2-(p-chlorophenyl)-1,2,4a,5,8,8a-hexahydro-4H-3,1-benzoxazines 12 and 13 are obtained. Surprisingly, the cis isomer 12 was found to be very unstable: the hetero ring suffered cleavage in solution even in the course of the ^{1}H NMR measurement.



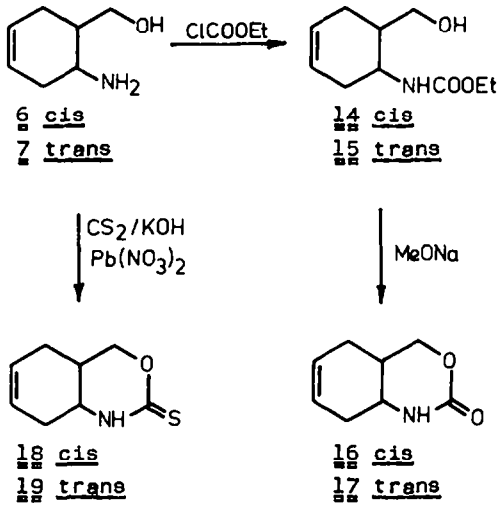
Scheme 2

^{1}H and ^{13}C observations (see below) indicate that the cyclization with aldehyde is stereospecific, and (in accordance with our earlier results[16]) of the two possible oxazine diastereomers, only the isomers containing H-2 and H-6 in the same steric situation* are formed.

*In earlier publications[2,9] we discussed the NMR data using a different numbering scheme. In the spectroscopic part of this paper, to facilitate comparison, the six atoms of the hetero ring are numbered consecutively, and the carbon atoms of the carbocycle are denoted by the numbers 7-10. (The spectroscopic numbering is shown in the Figure; for the chemical numbering see Scheme 2.)

For comparison with 12 and 13, the octahydro analogues 12a and 13a were also synthesized by the cyclization of cis- and trans-2-(hydroxymethyl)-1-cyclohexylamine[13] with p-chlorobenzaldehyde; the cis isomer 12a, similarly to 12, was found to be unstable. The structure of 13 was supported by X-ray diffraction analysis[17].

The aminoalcohols 6 and 7 were allowed to react with ethyl chloroformate to give the carbamates 14 and 15, which were cyclized with sodium methoxide to give cis- and trans-4a,5,8,8a-tetrahydro-4H-3,1-benzoxazin-2(1H)-ones 16 and 17 (Scheme 3). The corresponding cis- and trans-2-thiones, 18 and 19, were synthesized by the cyclization with lead(II) nitrate of the dithiocarbamates prepared from the aminoalcohols.



6 cis
7 trans

14 cis
15 trans

18 cis
19 trans

16 cis
17 trans

Scheme 3

Conformational analysis by ^{1}H and ^{13}C NMR spectroscopy

The IR, ^{1}H and ^{13}C NMR spectra unequivocally confirmed the structures suggested for the new compounds (see Tables 1 and 2). The predominant conformation of the flexible cis isomers was determined by utilizing the principles described in detail in connection with the conformational analysis of related compounds investigated earlier[8,9].

The derivatives described herein, being unsaturated in the carbocycle, have a more mobile ring system than the corresponding tetramethylene compounds; nevertheless, there are two relatively stable conformations in which the C_6-N bond is quasiaxial (relative to the near-boat cyclohexene ring) (Fig. A, B) in the structure corresponding to the N-inside conformation of the cyclohexane analogues, and quasiequatorial (Fig. C, D) in the compounds which correspond to the analogues present in the N-outside form. Owing to the presence of the sp^3 C-4 atom, with the exceptions of 8 and 9, the two stable conformations of the cyclohexene ring may each be combined with two inverse forms of the hetero ring; in the cases of compounds 10, 12, 16 and 18 this may result in four preferred conformations. The two inverse forms of the hetero ring differ in the dihedral angles made by C_5-H,C_4-Ha and C_5-H,C_4-He. In the structures corresponding to the N-inside form of cyclohexene, these angles are ~160° and ~40° (Fig. A) and ~45° and ~75° (Fig. B), respectively. The inversion of the hetero ring leaves the dihedral angles C_5-H,C_6-H (~10°), C_6-H,C_7-Ha and C_6-H,C_7-He (each ~60°) practically unaltered.

In the forms corresponding to the N-outside conformation (Fig. C, D) the C_6-N bond is quasiequatorial. The inversion of the hetero ring is actually a boat → twist flip. In the first case, when both rings have boat form (Fig. C), the C_5-H,C_4-Ha,e dihedral angles are ~180° and ~60°; in the other form (Fig. D) the angles are ~30° and ~90°. The C_5-H,C_6-H (~25°) and C_6-H,C_7-Ha,e (~180° and ~60°) dihedral angles are not changed considerably by inversion of the hetero ring in this case either.

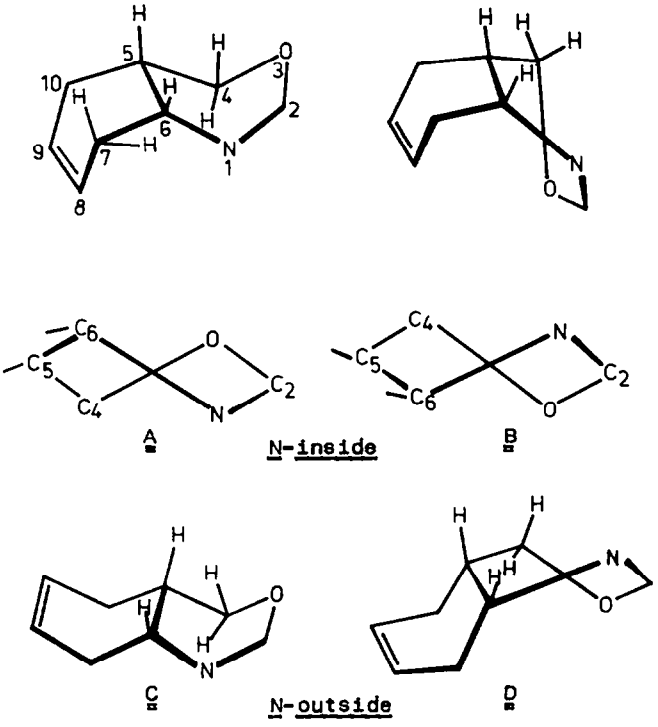


Fig.

Stable conformations of cis-anellated partially saturated benzoxazines 10, 12, 16 and 18

In the determination of the preferred conformation of the cis isomers, the decisive factors are the quasiaxial or quasiequatorial position of H-6 relative to the cyclohexene ring, and the H-4a,H-5, H-5,H-6 and H-6,7a,e dihedral angles; in the conformers illustrated by Fig. A, B and Fig. C, D these are the same as in the N-inside and N-outside forms of the tetramethylene analogues, respectively, and thus the latter notations will be adopted for the cyclohexene derivatives, with the tacit understanding that the latter can each be joined by two inverse forms of the hetero ring. Thus, the conformational relationships in compounds 8-11, 13, 13a and 16-19 can be described as follows.

From the ^{1}H NMR data on the pair of isomers 8 and 9, the significant differences in the chemical shifts and widths of the H-6 signals afford evidence of the preference of the N-inside conformation of the cis isomer 8. The paramagnetic shift of this signal by 0.45 ppm in 8 shows that H-6 is in the quasiequatorial position to the cyclohexene ring, in view of the empirical rule $\delta H_a < \delta H_e$, generally valid for cyclohexane derivatives[18a]. The very marked decrease of the halfbandwidth (about 10 Hz, instead of 35 Hz, in 8) is due to the fact that in the trans compound 9 there are H-5a,H-6a and H-6a,H-7a couplings which give rise to a large splitting according to the Karplus relation[19], whereas the equatorial-axial interactions in the cis isomer 8 involve much smaller coupling constants. Hence, in spite of the presence of two double bonds and a carbonyl group in the fused bicycle, the cis isomer 8 can be regarded as a conformationally homogeneous system, similar to the perhydro analogues, and the dominant conformer in this case too is the N-inside form.

As concerns the pair 10-11, the halfbandwidth of the H-6 signal in the ^{1}H NMR spectrum of the latter compound cannot be established, as the H-6 multiplet is overlapped by the signal of the light isotope contamination of the solvent; however, the 0.3 ppm paramagnetic shift of the H-6 signal observed for 10, and the considerable difference between the H-4a,H-5 coupling constants of the isomers (5.6 and 10.5 Hz) is unequivocal evidence of the preference of the N-inside conformation. The difference is due to the axial position of H-5, relative to the hetero ring, in the trans isomer, whereas in the cis counterpart (depending on the conformation of the hetero ring) this position is either quasiaxial or quasiequatorial. Therefore, the large diaxial interaction observed in 11 is substituted in the cis isomer 10 by axial-equatorial vicinal

couplings, resulting in smaller coupling constants (3.2 and 5.6 Hz; cf. Table 1). In view of the measured dihedral angles, conformation B can be considered probable. Actually, for A and C one of the coupling constants should be significantly greater to correspond to the dihedral angles 160° and 180°, respectively, whereas in structure D the coupling consistent with dihedral angle of 90° would not give rise to observable splitting.

The corresponding H-4a,H-5 coupling constants of 11.0 Hz in 13 and 13a can again be considered evidence of the trans anellation. The configuration at C-2 awaits elucidation in these compounds, though the equatorial position of the bulky p-chlorophenyl group, and consequently the axial position of H-2 is much more probable for energetic reasons. As the H-2 signal in the spectrum of 13 is a doublet with a coupling constant of 10 Hz, H-2 is obviously in the axial position, and therefore cis to H-6 and trans to H-5: a splitting of such magnitude can be brought about by vicinal NH,H-2 coupling only the presence of an axial H-2 atom. In deuteriochloroform the splitting due to the NH,H-2 coupling cannot be observed, owing to the increasingly rapid proton-exchange processes[18b,20], yet, on the basis of the identical H-2 signal shift, the analogous configuration of 13a is unambiguous.

The halfbandwidth (~10 Hz) of H-6 signal in the cis-1,3-oxazin-2-one and 2-thione derivatives, 16 and 18, as well as the 0.4 ppm paramagnetic shift of the H-6 signal compared with that in the trans counterparts, indicate preference of the analogous N-inside conformer. In view of the coupling constants given by the dt line distances, in the trans isomers the H-6 halfbandwidth is about 27 Hz.

As regards the conformation of the hetero ring, information can again be obtained from the H-4a,H-5 and H-4e,H-5 coupling constants, which are 3.0 and 4.5 Hz and 3.1 and 5.0 Hz for 16 and 18, respectively. The fact that these values are similar to those measured for compound 10 shows the probability of conformation B in this case too.

It is worthy of note that the chemical shift differences of the H-8 and H-9 olefin protons in 16 and 18 are greater than in the other compounds; one of the olefin hydrogens is more shielded by 0.1 ppm than its counterpart and than H-8 and H-9, which are equivalent in the trans isomers. This can be explained by the anisotropic effect of the C-N bond close to H-8 in the N-inside conformer.

The carbon resonance data (Table 2) support the above conclusions concerning the constitutions, configurations and conformations. The signal of C-2 in compounds 8-11, 16 and 17 is found in the shift region (152.2-154.1 ppm) characteristic of amide and urethane carbonyl carbons. In the spectra of 12a and 13a this signal is shifted to the region of saturated carbon atoms (89.4-88.4 ppm), and for 18 and 19 (186.9 ppm) the values are characteristic of thiourethanes.

The C-4 line in 8 and 9 is found where expected for an amide carbonyl group (174.3 and 174.4 ppm); in the spectra of the other compounds the corresponding O-methylene signal is observed between 69.4 and 75.4 ppm.

In the spectrum of the perhydro analogue 13a, the signals between 121.5 and 132.3 ppm of the olefin carbons of the former compounds are replaced by the lines due to C-7 and C-8 at 25.6 and 25.8 ppm. The four signals corresponding to the aromatic carbons in the other compounds are, of course, absent from the spectra of 16-19.

As evidence of the postulated configurations the C-4-C-10 atoms are considerably more shielded in the more crowded cis isomers 10, 16 and 18 than in their trans counterparts. With the exception of C-9, the diamagnetic shift of

Table 1. IR and ^{1}H NMR data on compounds 8-11, 13, 13a and 16-19

Compound	IR bands in KBr (cm^{-1})			^{1}H NMR chemical shifts[a] (δ_{TMS} = 0 ppm) at 250.14 MHz							
	νNH	νC=O	νC=N	OCH_2(2H)[b]	CH_2(7,10) m(4H)[c]	CH(5) m(1H)	=CH(8,9) ~e[d](2H)	H-6 m[e](1H)	NH(broad) s(1H)	ArH, 2x m (2x2H)[f]	
8	3245	1697	1639	-	1.9-2.5	2.75	5.65	4.00(10)	~10.65	~7.5[g],	7.85[h]
9	3220	1695	1639	-	2.1-2.8 m(5H)		5.73	3.55(35)	~10.75	7.45[g],	7.89[h]
10	-	-	1643	4.14 4.35	~1.9(3H), ~2.2(3H)	2.5[i]	5.60	3.76(5)	-	7.45,	7.85
11	-	-	1649	3.99 4.40	~1.8(3H), ~2.2(1H)	2.45[i]	5.72	~3.45[j]	-	7.55,	7.85
13[k]	3263	-	-	3.47 4.08	~1.6(2H), ~1.95(2H)	1.95	5.63	~2.8(25)		7.50,	7.60
13a[k]	3290	-	-	3.48 4.05	0.8-2.0 m(9H)[l]			2.54		7.30,	7.45
16	3217 3119	1699	-	4.18 4.28	~2.2 m(4H)	2.45	5.55[m] 5.68[m]	3.75(10)	~6.9	-	
17	3240	1697	-	3.98 4.32	1.6-2.4 m(5H)		5.68	3.34	~6.05	-	
18	3184	1306[n]	-	4.28 4.38	2.0-2.6 m(5H)		5.57[m] 5.67[m]	3.79(10)	~8.5	-	
19	3163	1385[n] 1373[n]	-	4.04 4.46	1.7-2.5 m(5H)		5.70	3.38	~8.2	-	

[a] In DMSO-d_6 (8-11, 13) or $CDCl_3$ (13a, 16-19). [b] 2xdd, or dd+t; A or B part of an ABX spin system; the J(AB), J(AX) and J(BX) coupling constants are (in Hz): 10.6, 3.2 and 5.6 (10), 10.5, 4.0 and 10.5 (11), 11.0, 3.8 and 11.0 (13), 11.0, 4.2 and 11.0 (13a), 11.0, 3.0 and 4.5 (16), 11.0, 4.1 and 11.0 (17), 11.2, 3.1 and 5.0 (18) and 11.1, 4.2 and 11.1 (19). [c] Partly or fully overlapping multiplets of the four (7a,e and 10a,e) protons. [d] Singulet-like AB part of an ABMNXY spin system. [e] Halfbandwidth (in Hz, in parentheses) of the dqs-like multiplets with coalesced lines (8-10, 13, 16 and 18) or dt with coupling constants (in Hz): 10.0, 10.0 and 3.6 (13a) and 10.5, 10.5 and 5.4 (17 and 19). [f] 2 + 3 H in case of 8 and 9; AA'BB' multiplet, $J_{AB} \approx 8$ Hz, δH-2',6') δH-3',5'. [g] Meta and para hydrogens. [h] Ortho protons. [i] Overlapped with the CHD_2 signal of the light isotope contamination of the solvent. [j] Overlapped with the water signal of the solvent. [k] H-2: 5.15 d, J(H-2, NH) = 10 Hz (13) and 5.16 ppm, s (13a), resp. [l] Overlapping multiplets of H-5, H-7a,e-H-10a,e. [m] The separated A and B parts of the ABMNXY spin system. [n] νC=S band, split in case of 19.

these carbon signals can also be observed in the case of **8**. This is due to the steric compression shift[21] causing increased shielding of carbon atoms to which sterically hindered groups are attached.

Finally, the dominant *N*-*inside* conformations are corroborated by the fact that in the pairs **16**-**17** and **18**-**19** the field effect is greater for C-6 (5.0 and 4.5 ppm) than for C-5 (3.0 ppm for both pairs); similarly, it is also larger for C-7 and C-8 than for the counterparts C-10 and C-9. This is explained by the position of the nitrogen atom better approaching the *axial* situation than does C-4. These differences are even greater in the case of the pair **8**-**9** (the steric compression shifts for the pairs C-5,6, C-7,10 and C-8,9 being 2.9 and 1.3, 6.1 and 3.3, 1.1 and -0.2 ppm, respectively), since in the *N*-*inside* form the *quasiaxial* nitrogen is very close to the "really" *axial* position; the C-N,C_5-H*a* and C-N,C_7-H*a* dihedral angles are $\sim 180^{\circ}$. In contrast, for the pairs

Table 2. ^{13}C NMR chemical shifts (δ_{TMS} = 0 ppm) for compounds **8**-**11**, **13**, **13a** and **16**-**19**[a]

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-1'	C-2',6'	C-3',5'	C-4'
8	152.9	174.3	38.4	53.1	29.2	126.1	132.3	23.7	135.2	129.8	128.7	127.0
9[b]	152.2	174.4	39.7	56.0	35.3	127.2	132.1	27.0	135.1	129.7	128.6	127.0
10	154.0	69.4	29.1	49.7	32.7	125.2[c]	126.1[c]	25.4	136.8	130.0	129.5	134.2
11	154.0	70.5	34.6	54.4	35.1	128.1[c]	126.9[c]	28.9	136.8	130.1	129.7	134.1
13	89.4	73.3	32.9	56.9	38.8	127.2		28.2	141.5	129.7[c]	129.4[c]	136.8
13a	88.4	72.6	43.3	60.2	32.9	25.6[c]	25.8[c]	27.1	139.4	127.5	128.3	133.8
16	153.9	69.5	22.5	46.4	29.4	121.5	124.0	27.8	-	-	-	-
17	154.1	75.4	25.5	51.4	33.3	124.1[c]	124.8[c]	31.6	-	-	-	-
18	186.9	72.9	24.2	48.8	29.1	123.7	126.2	28.2	-	-	-	-
19	186.9	73.0	27.2	53.3	33.7	126.0[c]	127.0[c]	32.1	-	-	-	-

[a] In DMSO-d_6 and $CDCl_3$ for **13a**, **16** and **17** at 20.14 MHz

[b] Order of carbons proved by DEPT measurement

[c] Reversed assignment is also possible

C-5,6 and C-7,10 in isomers 10-11, the situation is reversed and the difference between C-8,9 also disappears, for in conformation B the endocyclic C=N bond gives rise to deformation of the hetero ring; as a result, steric hindrance arises between the hydrogens attached to C-4 and C-10, and also between the O and C-9 atoms, owing to the proximity of the π-electrons.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded in $CDCl_3$ solution in a 5 mm tube at room temperature, on a Bruker WM-250 FT-spectrometer controlled by an Aspect 2000 computer at 250.13 MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters of the ^{1}H NMR spectra were as follows: sweep width 5 kHz, pulse width 1 μs (~20° flip angle), acquisition time 1.64 s, number of scans 16 or 32, computer memory 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement (LB: 0.7 Hz) was applied.

The ^{13}C NMR spectra were run in $CDCl_3$ solution in 5 or 10 mm tubes at room temperature, on a Bruker WP 80-SY FT-spectrometer with an Aspect 2000 computer at 20.14 MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were: sweep width 5 kHz, pulse width 3.5 μs (~30° flip angle), acquisition time 1.64 s, number of scans 2^9-2^{12} computer memory 16 K. Complete proton noise decoupling (~1.5 W) and Lorentzian exponential multiplication for signal-to-noise enhancement were used (line width 1.0 Hz).

DEPT[22] spectra were run in a standard way[23], using only the $\theta = 135^\circ$ pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively. Some lines overlapped by the strong signal of the DMSO-d_6 solvent thereby became clearly observable. Typical acquisition data were: number of scans 128-512, 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 a 3.7 ms delay for polarization.

cis-2-Amino-4-cyclohexene-1-carboxylic acid 1

cis-1,2,3,6-Tetrahydrophthalic anhydride (80.0 g) was added in portions to conc ammonium hydroxide (320 ml). The mixture was allowed to stand for 30 min, and then evaporated under reduced pressure. The residue was cooled to 10° and neutralized with 10 M HCl. The resulting solid was isolated by filtration with suction, washed with water and dried.

cis-1,2,3,6-Tetrahydrophthalic monoamide (50.76 g; 0.3 mol) was added in small portions to 2 N NaOHaq (120 ml). The solution was cooled to 0° and a mixture of 1 M sodium hypochlorite solution (370 ml) and 5 N NaOHaq (300 ml) was added dropwise, with stirring, the temperature being maintained at 0° throughout. The mixture was left to stand overnight, then kept at 70-75° for 10 min, cooled to ambient temperature, adjusted with 10 M HCl to pH 1.5, and evaporated to dryness. The residue was extracted with two 150 ml portions of hot EtOH, and the extract was evaporated. The residue was dissolved in a small amount of water and the hydrochloric acid was removed by means of a Dowex 50

ion-exchange column (acid cycle). Elution was effected with 1 M ammonium hydroxide solution (1000 ml). The dry residue of the eluate was dissolved in water; acetone was added until turbidity appeared, and the mixture was then allowed to stand in a refrigerator. The product was 28.5 g (67%) colourless, crystalline amino acid **1**, m.p. 216–218°.[24] (Found: C, 59.45; H, 7.77; N, 9.70. $C_7H_{11}NO_2$ requires: C, 59.56; H, 7.85; N, 9.92%.)

trans-2-Amino-4-cyclohexene-1-carboxylic acid **2**

A mixture of cis-1,2,3,6-tetrahydrophthalic anhydride (30.4 g; 0.2 mol), methanol (190 ml) and conc H_2SO_4 (2.3 ml) was refluxed for 4 h. The solvent was evaporated, and the residue was neutralized with dilute Na_2CO_3 solution and extracted with Et_2O. The extract was dried (Na_2SO_4), the solvent was evaporated, and the residue was subjected to fractional distillation. Dimethyl cis-1,2,3,6-tetrahydrophthalate (34.2 g; 86%) was isolated in this way, b.p. 97–99°/1 kPa.

A mixture of this product (29.7 g; 0.15 mol) and metallic sodium (0.15 g), dissolved in dry EtOH (2 ml), was heated on a steam-bath for 30 min. After cooling, 2% H_2SO_4 (50 ml) was added to the mixture. The phases were separated and the lower phase was mixed with 10% NaOHaq (100 ml). The mixture was stirred until homogeneity had been achieved (5–6 h), then acidified to pH 3 with 10 M HCl, and the trans-1,2,3,6-tetrahydrophtalic acid crystals which separated were filtered off, after 1 h, by suction. The product (22.6 g; 88.5%) had m.p. 161–163°.

The dry trans-1,2,3,6-tetrahydrophthalic acid (17.0 g; 0.1 mol) was dissolved in acetic anhydride (25 ml) at 60–70°. On cooling trans-1,2,3,6-tetrahydrophthalic anhydride (12.0 g; 79%) separated out, m.p. 158–160°. Evaporation of the mother liquor gave a second crop of the anhydride.

The amino acid **3** was prepared from trans-1,2,3,6-tetrahydrophthalic anhydride (15.2 g; 0.1 mol) in the same way as described for **1**. Colourless crystals (9.8 g; 69.5%) were obtained, m.p. 267–269°. (Found: C, 59.73; H, 7.73; N, 10.09. $C_7H_{11}NO_2$ required: C, 59.56; H, 7.85; N, 9.92%.)

cis- and trans-2-(Hydroxymethyl)-4-cyclohexenyl-1-amine **6** and **7**.

Lithium aluminium hydride (14.0 g; 0.37 mol) was added in portions to dry tetrahydrofuran (800 ml), with cooling and stirring. This was followed by the gradual addition of the amino acid **1** or **3** (18.8 g; 0.133 mol), and the mixture was refluxed for 20 h. After cooling to 0°, the excess of lithium aluminium hydride was decomposed by the dropwise addition of water (30 ml), and the mixture was stirred until a white suspension had formed. The solide were removed by filtration with suction, the solvent was evaporated and the oily residue was subjected to fractional distillation. In this way, product **6** (16.1 g; 95%), b.p. 103–105°/530 Pa, or compound **7** (11.5 g; 68%), b.p. 105–107°/530 Pa, was obtained. (Found for **6**: C, 66.25; H, 10.54; N, 10,78; for **7**: C, 66.17; H, 10.32; N, 11.17. $C_7H_{11}NO$ requires: C, 66.10; H, 10.30; N, 11.01%.)

cis- and trans-2-Phenyl-4a,5,8,8a-tetrahydroquinazolin-4(3H)-one **8** and **9**

The amino acid **1** or **3** (1.41 g; 0.01 mol) and ethyl benzimidate (1.49 g; 0.01 mol) were refluxed in chlorobenzene (50 ml) for 20 h. The residue resulting from evaporation of the reaction mixture was crystallized. The properties of the colourless crystalline compounds **8** and **9** are listed in Table 3.

Table 3. Physical and analytical data on the compounds prepared (8-19)

Compound	M.p. °C	Yield %	Found % C	H	N	Formula	Required % C	H	N
8	166-168[a]	65	74.46	6.30	12.44	$C_{14}H_{14}N_2O$	74.31	6.24	12.38
9	231-233[b]	62	74.51	6.16	12.48	$C_{14}H_{14}N_2O$	74.31	6.24	12.38
10	82-84[c]	45	68.03	5.85	5.61	$C_{14}H_{14}NClO$	67.88	5.70	5.65
11	93-95[d]	56	68.11	5.86	5.57	$C_{14}H_{14}NClO$	67.88	5.70	5.65
12	75-77[c]	40	67.17	6.28	5.50	$C_{14}H_{16}NClO$	67.34	6.46	5.61
13	83-85[c]	38	67.25	6.30	5.73	$C_{14}H_{16}NClO$	67.34	6.46	5.61
12a	62-63[e]	54	66.63	7.05	5.40	$C_{14}H_{18}NClO$	66.79	7.21	5.56
13a	107-108[c]	50	66.71	7.13	5.52	$C_{14}H_{18}NClO$	66.79	7.21	5.56
14	71-72[f]	85	60.40	8.71	6.82	$C_{10}H_{17}NO_3$	60.28	8.60	7.03
15	71-72[f]	77	59.97	8.58	7.16	$C_{10}H_{17}NO_3$	60.28	8.60	7.03
16	113-114[b]	68	62.62	7.19	9.25	$C_8H_{11}NO_2$	62.73	7.24	9.15
17	190-191[b]	72	62.58	7.38	9.21	$C_8H_{11}NO_2$	62.73	7.24	9.15
18	162-164[d]	45	56.61	6.36	8.42	$C_8H_{11}NOS$	56.77	6.55	8.28
19	242-244[d]	49	56.83	6.71	8.41	$C_8H_{11}NOS$	56.77	6.55	8.28

[a]From diisopropyl ether. [b]From ethyl acetate. [c]From benzene - petroleum ether. [d]From ethanol. [e]From petroleum ether. [f]From ethyl acetate - petroleum ether.

cis- and trans-2-(p-Chlorophenyl)-4a,5,8,8a-tetrahydro-4H-3,1-benzoxazine 10 and 11

The aminoalcohol 6 or 7 (1.3 g; 0.01 mol) and ethyl p-chlorobenzimidate (1.8 g; 0.01 mol) were refluxed in EtOH (50 ml) for 6 h. The residue obtained on evaporating the reaction mixture was crystallized. The data on the products 10 and 11 are given in Table 3.

cis- and trans-2-(p-Chlorophenyl)-1,2,4a,5,8,8a-hexahydro-4H-3,1-benzoxazine 12 and 13 and cis- and trans-2-(p-chlorophenyl)perhydro-3,1-benzoxazine 12a and 13a

The aminoalcohol 6 or 7 (1.3 g; 0.01 mol) or cis- or trans-2-(hydroxymethyl)cyclohexylamine was mixed with p-chlorobenzaldehyde (1.4 g; 0.01 mol) in dioxane (50 ml), one drop of ethanol saturated with HCl was added, and the mixture was refluxed for 5 h. It was then evaporated and the residue was crystallized, to yield a colourless product. The properties of the compounds are shown in Table 3.

cis- and trans-4a,5,8,8a-Tetrahydro-4H-3,1-benzoxazin-2(1H)-one 16 and 17

The aminoalcohol 6 or 7 (1.3 g; 0.01 mol) and $NaHCO_3$ (0.84 g; 0.01 mol) were dissolved in water (10 ml), ethyl chloroformate (1.1 g; 0.01 mol) was added dropwise, and the mixture was refluxed for 30 min. After cooling, the solution was extracted with Et_2O, the extract was dried (Na_2SO_4) and the solvent was evaporated. Dissolution of the residue in a mixture of ethyl

acetate and petroleum ether and refrigeration of the solution gave **14** and **15** as colourless crystals.

The carbamate **14** or **15** (2.0 g; 0.01 mol) was heated with sodium methoxide (50 mg) in an oil bath at 200° for 1 h. The melt was extracted with ethyl acetate and the product **16** or **17** obtained from the extract was crystallized. The data on compounds **14**-**17** are listed in Table 3.

cis- and trans-4a,5,8,8a-Tetrahydro-4H-3,1-benzoxazine-2(1H)-thione **18** and **19**

The aminoalcohol **6** or **7** (2.1 g; 0.0165 mol) and KOH (1.1 g) were dissolved in water (10 ml) and the solution was cooled to 0°. A solution of carbon disulphide (1.3 g) in dioxane (8 ml) was added dropwise, with stirring, and the mixture was stirred for 5 min. Aqueous solutions of KOH (0.55 g in 10 ml) and then lead(II) nitrate (5.5 g in 30 ml) were added and the mixture was stirred at 60° for 10 min. The lead sulphide was filtered off; evaporation of the filtrate gave a solid product. The properties of **18** and **19** are shown in Table 3.

REFERENCES

[1] Part 82: G. Bernáth and F. Fülöp, *Pharmazie*, **39**, 531 (1984); Part 75: K. Csukonyi, J. Lázár, G. Bernáth and I. Hermecz, *Monatsh. Chem.*, to be published.

[2] G. Bernáth, F. Fülöp, L. Gera, L. Hackler, A. Kálmán, Gy. Argay and P. Sohár, *Tetrahedron*, **35**, 799 (1979).

[3] G. Bernáth, K. L. Láng, K. Kovács and L. Radics, *Acta Chim. Acad. Sci. Hung.*, **73**, 81 (1972).

[4] G. Bernáth, Gy. Göndös, K. Kovács and P. Sohár, *Tetrahedron*, **29**, 981 (1973).

[5] G. Stájer, A. E. Szabó, F. Fülöp, G. Bernáth and P. Sohár, *Heterocycles*, **19**, 1191 (1982).

[6] G. Stájer, A. E. Szabó, F. Fülöp, G. Bernáth, A. Kálmán, Gy. Argay and P. Sohár, *Tetrahedron*, **39**, 1829 (1983).

[7] G. Bernáth, F. Fülöp, Gy. Jerkovich and P. Sohár, *Acta Chim. Acad. Sci. Hung.*, **101**, 61 (1979).

[8] P. Sohár and G. Bernáth, *Org. Magn. Reson.*, **5**, 159 (1973).

[9] P. Sohár, L. Gera and G. Bernáth, *Org. Magn. Reson.*, **14**, 204 (1980); F. Fülöp, G. Bernáth, Gy. Argay, A. Kálmán and P. Sohár, *Tetrahedron*, **40**, 2053 (1984).

[10] Gy. Argay, A. Kálmán, F. Fülöp and G. Bernáth, *Acta Chim. Acad. Sci. Hung.*, **109**, 39 (1982).

[11] Á. Kapor, B. Ribár, A. Kálmán, Gy. Argay, G. Stájer and G. Bernáth, *Cryst. Struct. Commun.*, **11**, 1777 (1982); Gy. Argay, A. Kálmán, B. Ribár, F. Fülöp and G. Bernáth, *Cryst. Struct. Commun.*, **11**, 959 (1982).

[12] G. Bernáth, L. Gera, Gy. Göndös, M. Hermann, M. Szentiványi, Z. Ecsery and E. Janvári, *German Pat.* 2,643,384; *Chem. Abstr.*, **87**, 168078b (1977).

[13] G. Bernáth, K. Kovács and K. L. Láng, *Acta Chim. Acad. Sci. Hung.* **64**, 183 (1970).

[14] P. Bod, personal communication.

[15] W. Hückel and E. Got, *Ber. dtsch. Chem. Ges.*, **58**, 449 (1925).

[16]G. Bernáth, F. Fülöp, A. Kálmán, Gy. Argay, P. Sohár and I. Pelczer, Tetrahedron, 40, 3587 (1984)
[17]Gy. Argay, B. Ribár, A. Kálmán, G. Stájer and G. Bernáth, to be published.
[18]P. Sohár, Nuclear Magnetic Resonance Spectroscopy, CRC Press, Boca Raton, Florida (1983). (a) Vol. 2, p. 27, (b) Vol. 2, p. 94.
[19]M. Karplus, J. Chem. Phys., 30, 11 (1959); 33, 1842 (1960).
[20]H. S. Gutowsky, D. W. McCall and C. P. Slichter, J. Chem. Phys., 21, 279 (1953).
[21]D. M. Grant and B. V. Cheney, J. Am. Chem. Soc., 89, 5315 (1967).
[22]D. T. Pegg, D. M. Doddrell and M. R. Bendall, J. Chem. Phys., 77, 2745 (1982).
[23]M. R. Bendall, D. M. Doddrell, D. T. Pegg and W. E. Hull, High Resolution Multipulse NMR Spectrum Editing and DEPT. Bruker, Karlsruhe (1982).
[24]H. R. Kricheldorf, Justus Liebigs Ann. Chem., 1387 (1975) give m.p. 265–268°, including reference to the work of E. J. Moriconi and P. H. Mazzocchi, J. Org. Chem., 31, 1372 (1966), claiming that in the latter paper a similar m.p. (269–271°) was given. However, in this latter work such a m.p. is not reported at all.