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Stereochemical Studies 98. Saturated Heterocycles 100 [1]. Synthesis of Stereoisomeric 2-Ethylimino-3,1-perhydrobenzoxazines and Benzothiazines

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With ethyl isothiocyanate, the stereoisomeric *cis*- and *trans*-2-hydroxymethyl-1-cyclohexylamines and their *N*-methyl and *N*-benzyl derivatives (**4a–c**, **5a–c**) furnished the corresponding thiocarbamates (**6a–c**, **7a–c**). Treatment of compounds **6** and **7** with methyl iodide and subsequent alkali treatment afforded 3,1-perhydrobenzoxazines **8a–c**, **9a–c**, while cyclization of compounds **6** and **7** to the 3,1-perhydrobenzothiazines **10a–c**, **11a–c** was performed with HCl. It was found that the predominant conformation of the *N*-unsubstituted *cis* isomers **8a** and **10a** is the *N-inside* form, while the *N*-substituted derivatives **8b, c** and **10b, c** have the *N-outside* preferred conformation.

(Keywords: 3,1-Perhydrobenzoxazines; 3,1-Perhydrobenzothiazines; Conformational analysis)

Stereochemische Untersuchungen, 98. Gesättigte Heterocyclen, 100. Synthese von stereoisomeren 2-Ethylimino-3,1-perhydrobenzoxazinen und benzothiazinen

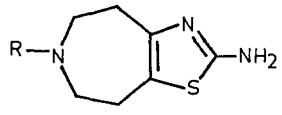
Aus den stereoisomeren *cis*- und *trans*-2-Hydroxymethyl-1-cyclohexylaminen und ihren *N*-Methyl- und *N*-Benzylderivaten (**4a—c**, **5a—c**) wurden mit Ethylisothiocyanat die entsprechenden Thiocarbamate (**6a—c**, **7a—c**) erhalten. Behandlung der Verbindungen **6** und **7** mit Methyljodid und anschließend Alkali ergab die 3,1-Perhydrobenzoxazine **8a—c**, **9a—c**, während mit HCl die Cyclisierung zu den 3,1-Perhydrobenzothiazinen **10a—c**, **11a—c** eintrat. Es wurde festgestellt, daß die bevorzugte Konformation der *N*-unsubstituierten *cis*-Isomeren **8a** und **10a** die *„N-innen"*-Form ist, während die der *N*-substituierten Derivate **8b, c** und **10b, c** bevorzugt in der *„N-außen"*-Form vorliegen.

Introduction

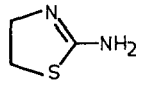
In recent years, numerous cyclic guanidine derivatives (*e.g.* clonidine) have been introduced as drugs [2]. Further, research on analogous heterocycles, having oxygen or sulphur atoms instead of nitrogen in the

ring, has become more intense. These types of molecules are important both for pharmacological purposes [2, 3] and from a theoretical point of view (*e.g.* amino ⇌ imino tautomerism) [4]. The condensed-skeleton thiazolines of type **1** include α-adrenoceptor agonists, while some of the 2-aminothiazolines (*e.g.* revercan) are compounds possessing properties inducing the reverse transformation of cancer cells [3].

In a continuation of our systematic synthetic and stereochemical work on bicyclic condensed-skeleton 1,3-heterocycles containing two heteroatoms [5–7], our present aim was the synthesis of stereoisomeric 3,1-perhydrobenzothiazines (**10**, **11**) and 3,1-perhydrobenzoxazines (**8**, **9**). We have recently reported on the synthesis of analogous 2-phenylimino-1,3-perhydrobenzoxazines (**3**) and their homologues containing a cyclopentane ring [7].



1a: R = $CH_2C_6H_4Cl$(p)
1b: R = $CH_2CH{=}CH_2$



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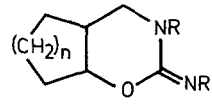


cis or trans; n = 1, 2
R = H, CH_3, $CH_2C_6H_5$

3

It was shown earlier that in analogous 3,1-benzoxazines and their homologues the predominant conformation of the *cis* isomers depends on the annelated substituent, and in the preferred conformation the bulky substituent occupies the *equatorial* position [8].

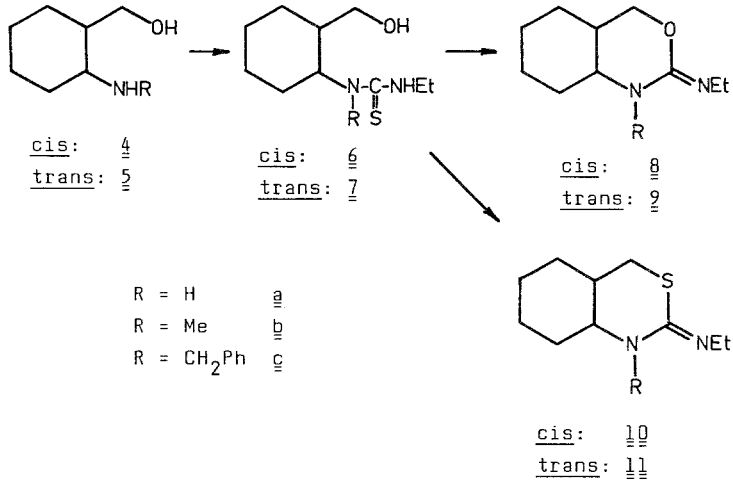
Besides the synthetic interest, the synthesis of compounds **8**–**11** seemed worthwhile in order to study the influence of substituents attached to the nitrogen on the predominant conformation. The *trans* and *cis* derivatives were therefore prepared from the precursors with $R = H$, CH_3 or $CH_2C_6H_5$.

Results and Discussion

Syntheses

The synthetic routes are shown in the formula scheme. *cis*- and *trans*-2-hydroxymethyl-1-cyclohexylamines (**4a**, **5a**) and their *N*-methyl and *N*-benzyl derivatives were prepared from the corresponding β-amino acids and their *N*-acyl derivatives by reduction with lithium aluminium hydride [5]. In the reactions with ethyl isothiocyanate in ether at ambient temperature, the aminoalcohols of types **4**, **5** selectively furnished the corresponding thiocarbamides **6a–c**, **7a–c**. Compounds **6**, **7** with methyl

iodide gave thioethers, which were transformed in alkaline medium, without isolation, to the 3,1-perhydrobenzoxazines **8a–c**, **9a–c** by the elimination of methyl mercaptan [9]. When thiocarbamides **6**, **7** were refluxed with HCl in ethanol, the analogous 3,1-perhydrobenzothiazines could be obtained [9–11].



Compounds of type **3** were earlier prepared from the corresponding thiocarbamide or carbamide derivatives [7]. It was found that in the former reaction the reaction rate depends significantly on the configuration of the starting materials, on the substituents of nitrogen and on the reaction conditions.

From the thiocarbamides **6a–c**, **7a–c**, the oxazines **8a–c**, **9a–c** and thiazines **10a–c**, **11a–c** were prepared in good yields (62–89%), independently of the substituents and configuration.

Spectroscopic Studies

The configurations and conformations of the compounds were established by ^{1}H NMR spectroscopy. The NMR analysis was performed similarly as reported earlier [8, 12, 13]. The configurations of the two isomers were determined on the basis of the significant chemical shift differences of the A, B, M and X protons, and through the differences in the indirect couplings. Moreover, in analogy to previous studies, the preference for one of the forms in the conformational equilibrium of the *cis* compounds could be determined. Two extreme cases of this equilibrium could be observed in $CDCl_3$, depending on the substituents of the hetero ring [14, 16] (Fig. 1). The NMR parameters of these two cases—the

nitrogen atom of the hetero ring is *axial* or *equatorial* with respect to the cyclohexane ring—are different. In the oxazines having the *N-inside* predominant conformation, the chemical shift difference of the A and B protons is probably small—both of them are diamagnetically shifted by ring protons. The X proton has a large downfield shift: the paramagnetic shielding of the nitrogen is only compensated by a weak diamagnetic

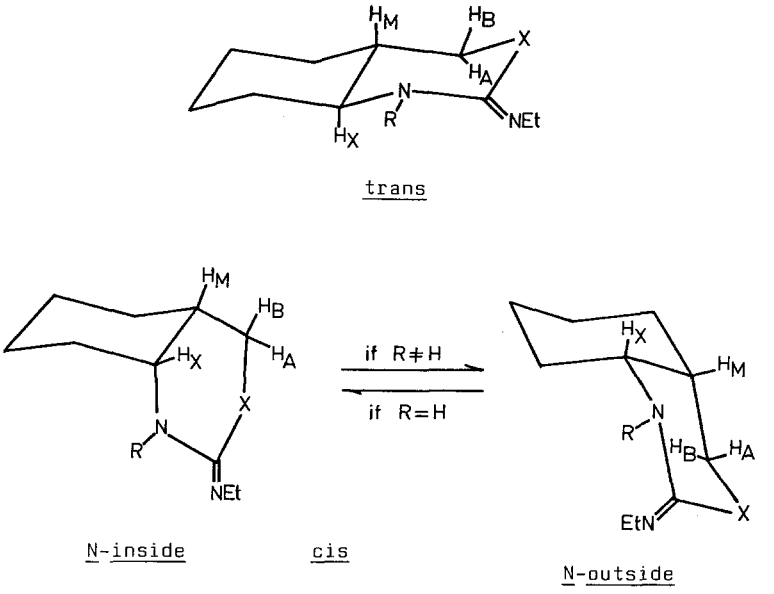


Fig. 1

interaction. The indirect couplings of the A proton are almost equivalent to those of the B proton. The half-band-width of the X proton is 10–15 Hz, as a consequence of the small vicinal couplings.

The NMR parameters of the compounds having the *N-outside* predominant conformation differ from those in the previous case: the chemical shift difference of the A and B protons is large, in accordance with the non-equivalent diamagnetic shielding, and thus $\delta_A < \delta_B$. The X proton has a smaller down-field shift, corresponding to the decreasing effect of the *axial* ring protons on the paramagnetic shielding. The couplings of the A and B protons are significantly different. The half-band-width of the A proton is 16–25 Hz, the broadening being a consequence of the *diaxial* coupling.

The *trans* isomers were identified through the characteristic parameters δ_A, δ_B, δ_X, J_{A-M}, J_{B-M} and $\Delta\nu(1/2)_X$ and through the envelope of the signal of the carbocyclic ring protons. The NMR data supported the

Table 1. *Characteristic chemical shifts and coupling constants of compounds* **8 a–c—11 a–c**

Compound	Chemical shifts (δ, ppm)						Coupling constants (Hz)			
	H_A	H_B	H_X	CH_2CH_3	CH_2CH_3	R[a]	J_{AB}	J_{AM}	J_{BM}	$\Delta\nu_{1/2}$[b]
8 a	3.9[c]	3.9[c]	3.3	3.1	1.1	3.6	—	4.5	4.5	12
8 b	3.9	4.1	3.1	3.0	1.0	2.8	10.5	5	10.5	17
8 c	3.9	4.2	2.2	3.2	1.1	7.3, 5.2, 4.1	9	5	9	22
9 a	4.1	3.7	3.3	3.1	1.1	3.9	10	4.5	10	27
9 b	3.9	3.6	[c]	3.0	1.1	2.8	10.5	4.5	10.5	[d]
9 c	4.0	3.6	2.8	3.2	1.1	7.3, 5.1, 4.1	10.5	4	10.5	[e]
10 a	3.0[c]	3.0[c]	3.5	3.2	1.1	3.8	—	4.5	4.5	10
10 b	2.4	3.4	3.1	3.3	1.2	3.0	12	4.5	12	[d]
10 c	2.5	3.3	3.0	3.2	1.1	7.3, 5.5, 4.0	12	2	12	[d]
11 a	2.7	2.5	2.9	3.2	1.2	3.0	9	4.5	9	[d]
11 b	2.7	2.5	2.9	3.2	1.2	2.9	9	4.5	9	[d]
11 c	2.7	2.5	2.9	3.2	1.1	7.3, 5.3, 4.4	9	4.5	9	[d]

[a] R = H, CH_3 or $CH_2C_6H_5$, respectively
[b] Half-band-width
[c] AA′ part of spectra
[d] Overlapping multiplets
[e] Couplings: 10 Hz, 10 Hz, 3 Hz

configurations of the *cis* and *trans* isomers which were to be expected from their synthesis. The *cis* and *trans* configurations and the stereohomogeneity are therefore unambiguous (Table 1). The NMR analysis of the related derivatives indicated that the predominant conformation of the *cis* isomer **1** is *N-inside,* while that of compounds **2** and **3** is *N-outside.*

The related thiazines show similar spectroscopic characteristics, although the NMR spectra are crowded, due to the decreased paramagnetic shielding of the sulphur. Therefore, the exact parameters cannot be determined at 60 MHz, though the configuration, which also followed from the mode of synthesis, could be identified unambiguously (see Table 1).

Experimental

M.p.'s were determined with a *Boetius* micro melting point apparatus and are uncorrected. The physical properties, analyses and yields of the compounds prepared are listed in Table 2.

The ^{1}H NMR spectra were recorded in continuous wave mode at ambient temperature, with an external H_2O lock, at 60 MHz, using a JEOL C HL 60 spectrometer. The chemical shifts were determined on the δ scale in ppm, *TMS* being used as internal standard (Table 1).

Table 2. *Data for compounds* **6 a–c—11 a–c**

Compound	Yield (%)	M.p. (°C) (Solvent)	Formula[b] (Mol. wt.)
6 a	88	122–124 (benzene)	$C_{10}H_{20}N_2OS$ (216.35)
6 b	83	64–67 (benzene)	$C_{11}H_{22}N_2OS$ (230.38)
6 c	72	140–142 (benzene)	$C_{17}H_{26}N_2OS$ (306.45)
7 a	78	99–101 (ethyl acetate)	$C_{10}H_{20}N_2OS$ (216.35)
7 b	75	122–124 (benzene)	$C_{11}H_{22}N_2OS$ (230.38)
7 c	80	104–107 (ethyl acetate)	$C_{17}H_{26}N_2OS$ (306.45)
8 a	70	85–87 (petrol. ether)	$C_{10}H_{18}N_2O$ (182.26)
8 b[a]	62	95–97 (ethanol)	$C_{17}H_{23}N_5O_8$ (425.39)
8 c[a]	73	132–134 (ethanol)	$C_{23}H_{22}N_5O_8$ (495.45)
9 a	68	82–83 (petrol. ether)	$C_{10}H_{18}N_2O$ (182.26)
9 b[a]	65	101–103 (ethanol)	$C_{17}H_{23}N_5O_8$ (425.39)
9 c	77	88–90 (petrol. ether)	$C_{17}H_{24}N_2O$ (272.38)
10 a[a]	80	127–130 (ethanol)	$C_{16}H_{21}N_5O_7S$ (427.44)
10 b[a]	83	119–121 (ethanol)	$C_{17}H_{23}N_5O_7S$ (441.46)
10 c	89	71–73 (petrol. ether)	$C_{17}H_{24}N_2S$ (288.45)
11 a[a]	85	130–132 (ethanol)	$C_{17}H_{21}N_5O_7S$ (427.44)
11 b[a]	87	145–147 (ethanol)	$C_{17}H_{23}N_5O_7S$ (441.46)
11 c	85	74–76 (petrol. ether)	$C_{17}H_{24}N_2S$ (288.45)

[a] Picrate

[b] The analytical data for C, H, N, S agree with the molecular formulas

Preparation of Thioureas **6 a–c** *and* **7 a–c**

Aminoalcohol **4 a–c** or **5 a–c** (10 mmol) was dissolved in 30 ml ether, and ethyl isothiocyanate (10 mmol, 8.8 ml) was added. After standing for 3 h at room temperature, the crystalline product was filtered off and recrystallised.

Preparation of 2-Ethylimino-perhydro-3,1-benzoxazines (**8 a–c**, **9 a–c**)

Thiourea **6 a–c** or **7 a–c** (5 mmol) was dissolved in methanol (10 ml), 1 ml methyl iodide was added and the solution was stirred for 2 h. After evaporation, the yellow oily residue was dissolved in 20 ml methanol containing 3 g potassium hydroxide. The solution was stirred for 3 h (elimination of methyl mercaptane took place) and then evaporated. The residue was dissolved in water (30 ml) and extracted with chloroform. After drying and evaporation of the organic phase, a crystalline product was formed. If the product was an oil, the picrate salt was prepared for analysis. For spectroscopic investigation, the base was liberated from the picrate salt with sodium hydroxide solution.

Preparation of 2-Ethylimino-perhydro-3,1-benzothiazines (**10 a–c**, **11 a–c**)

Thiourea **6 a–c** or **7 a–c** (5 mmol) was refluxed in ethanol (25 ml) containing 10% dry hydrogen chloride for 25 min. After evaporation of the ethanol, the residue was neutralised with 10% potassium hydroxide and extracted with chloroform. After drying and evaporation of the organic phase, a crystalline product was formed. If the product was an oil, the picrate salt was prepared for analysis.

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