STEREOCHEMICAL COURSE OF THE REACTION OF 2-HALOETHYL ISOTHIOCYANATES WITH NUCLEOPHILES. STEREOSPECIFIC ROUTE TO 4,5-DISUBSTITUTED Δ^2-THIAZOLINES AND THIAZOLIDINE-2-THIONES

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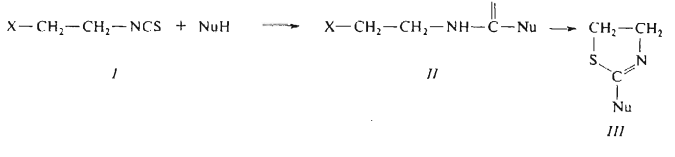
Diastereoisomeric 1-chloro-1-phenyl-2-isothiocyanatopropanes have been prepared. They reacted stereospecifically with CH_3ONa, diethylamine, aniline and NaSH to give pure *cis* or *trans*-4,5-disubstituted Δ^2-thiazolines and thiazolidine-2-thiones whose configuration was determined using the nuclear Overhauser effect. The preponderant conformation of diastereoisomeric 1-chloro-1-phenyl-2-isothiocyanatopropanes was estimated on the basis of coupling constants of vicinal protons.

2-Haloethyl isothiocyanates *I* react readily with various nucleophiles such as amines, thiolates, alkoxides or carbanions in an alkaline medium giving rise[1,2] to Δ^2-thiazoline derivatives *III*. If hydrosulfide ion is used as nucleophile, this reaction leads to thiazolidine-2-thione derivatives[3]. According to the existing evidence, the first reaction step is a nucleophilic addition to the NCS group, leading to an intermediate (such as *e.g. II*) which is further cyclized at the sulfur atom, as described in Scheme1. This reaction course is supported also by the fact that if hydroselenide ion is used as nucleophile, the intermediate *II* is selenothiocarbamate which undergoes cyclization at the more nucleophilic selenium atom to give selenoazolidine-2-thione[3].



I *II* *III*

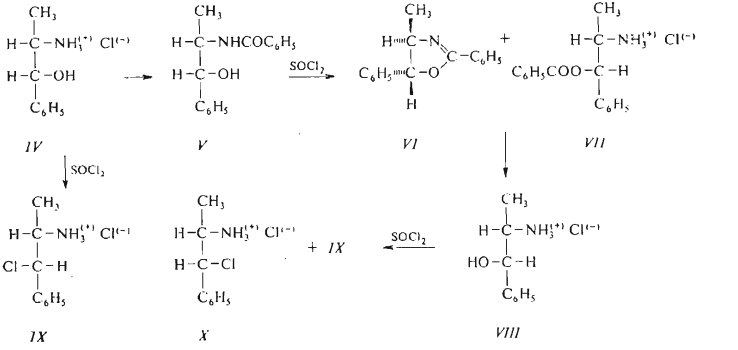
SCHEME 1

We assume that the cyclisation, depicted in Scheme 1, proceeds by an intramolecular S_N2 mechanism with inversion of configuration at the halogen-bearing carbon atom. Such reaction should be stereospecific and thus diastereoisomerically pure 2-haloethyl isothiocyanates *I*, substituted on both carbon atoms, should afford diastereoisomerically pure thiazolines *III*. We found only one mention in the literature on the stereochemical course of an analogous reaction. Woodgate and coworkers[2] obtained *cis*-cyclohexanothiazoline derivatives by reaction of *trans*-1-iodo-2-isothiocyanatocyclohexane with amines; however, they did not investigate whether the reaction was completely stereospecific, (*i.e.* whether also small amount of the *trans*-isomer was formed.

Of reactions affording 1,3-thiazolidine-2-thione or its derivatives[3-8], only three have been studied from the point of view of stereospecificity. Dewey and Bafford[5] observed that reaction of 2-aminoethyl sulfates with potassium ethyl xanthogenate proceeds by two competing mechanisms and gives a mixture of two stereoisomeric 4,5-disubstituted 1,3-thiazolidine-2-thiones. Foglia and coworkers[7] studied the reaction of aziridines with carbon disulfide and found that whereas *trans*-4,5-disubstituted 1,3-thiazolidine-2-thiones are formed stereospecifically, the corresponding *cis*-isomers contain as much as 8% of the *trans*-isomer. Probably, the only hitherto known stereospecific reaction leading to pure stereoisomers of 4,5-disubstituted 1,3-thiazolidine-2-thiones is the reaction of substituted 1-isothiocyanato-2-ethyl thiocyanates with alkoxides[8].

In order to check the steric course of reaction of 2-haloethyl isothiocyanates with nucleophilic reagents, we synthesized the diastereoisomeric 1-chloro-1-phenyl-2-isothiocyanatopropanes. We started from the described[9] mixture of diastereoisomeric 2-amino-1-phenylpropan-1-ols from which the *erythro*-isomer *IV* was obtained by crystallization of hydrochlorides from a mixture of ethanol and ethyl acetate. Reaction of the N-benzoyl derivative *V* with thionyl chloride[10] afforded a mixture of *trans*-2,5-diphenyl-4-methyl-1,3-oxazoline (*VI*) and *threo*-1-benzoyloxy-1-phenyl-2-propylammonium chloride (*VII*) which was hydrolyzed to afford pure *threo*-2-amino-1-phenylpropan-1-ol (*VIII*) (Scheme 2). We tried to convert both the pure diastereoisomeric amino alcohols *IV* and *VIII* to pure diastereoisomers of 1-chloro-1-phenyl-2-propylammonium chloride by reaction with thionyl chloride. Whereas the *erythro*-isomer *IV* gave pure *threo*-1-chloro-1-phenyl-2-propylammonium chloride (*IX*), m.p. 212–213°C, reaction of the corresponding *threo*-isomer *VIII* was not stereospecific, affording a mixture of *threo*- and *erythro*-1-chloro-1-phenyl-2-propylammonium chloride in the ratio *IX* : *X* = 2·15 : 1 (according to ^{1}H-NMR spectroscopy). A mixture of the diastereoisomers *IX* and *X* was formed also in reaction of *VII* with thionyl chloride in the presence of pyridine, as well as on treatment with phosphorus pentachloride or trichloride. Phosphorus trichloride proved to be the reagent of choice: it gave a 1 : 4 mixture of *IX* and *X* from which the pure *erythro*-isomer *X* (m.p. 173–174·5°C) was obtained by crystallization. The pure diastereo-

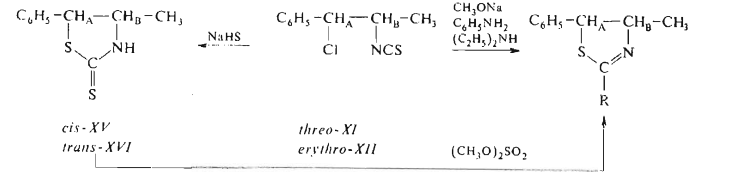
isomers *IX* and *X* have not been prepared previously; they were obtained[11] only as a mixture and assigned configuration only on the basis of coupling constants of vicinal protons in ^{1}H-NMR spectrum (*IX*: 9·6 Hz,, *X*: 4·6 Hz).



IV *V* *VI* *VII* *IX* *X* *VIII*

SCHEME 2

Treatment of *threo*-1-chloro-1-phenyl-2-propylamine with thiophosgene afforded pure 1-chloro-1-phenyl-2-isothiocyanatopropane (*XI*) of the same configuration as the starting compound *IX*. Also the *erythro*-isomer *X* on reaction with thiophosgene gave pure *erythro*-1-chloro-1-phenyl-2-isothiocyanatopropane (*XII*). It is, however, more economical to prepare the mixture of *XI* and *XII* (1 : 4) from a mixture of amines *IX* and *X* (after reaction of *VIII* with PCl_3) and to isolate the pure *erythro*-isomer *XII* by chromatography on a column of silica gel.



cis-*XV* *trans*-*XVI* *threo*-*XI* *erythro*-*XII*

R	OCH_3	NHC_6H_5	$N(C_2H_5)_2$	SCH_3
cis	*XIII*	*XVII*	*XIX*	*XXI*
trans	*XIV*	*XVIII*	*XX*	*XXII*

SCHEME 3

Each of the diastereoisomers *XI* and *XII* was subjected to reaction with NaHS, CH_3ONa, aniline and diethylamine (Scheme 3). The products of reaction with CH_3ONa were volatile enough to allow gas–liquid chromatographic analysis which showed that the obtained products *XIII* and *XIV* were sterically completely homogeneous. *i.e.* that the reaction was completely stereospecific. Analogously, the crude 5-phenyl-4-methyl-1,3-thiazolidine-2-thiones *XV* and *XVI* on treatment with dimethyl sulfate were transformed into the corresponding 2-methylthio-Δ^2-thiazoline derivatives *XXI* and *XXII* under conditions ensuring retention of configuration[7,8]. Gas–liquid chromatography proved that the products *XXI* and *XXII* are diastereoisomerically pure and thus the reaction of *XI* and *XII* with NaSH was shown to be stereospecific. Since other products prepared, *i.e.* 5-phenyl-2-phenylamino-4-methyl--1,3-thiazolines (*XVII* and *XVIII*) and 2-diethylamino-5-phenyl-4-methyl-1,3-thiazolines (*XIX* and *XX*), were not volatile enough, their stereochemical purity was checked by ^{1}H-NMR spectroscopy (200 MHz). The above-mentioned results confirm that cyclisation of the intermediate *II* to *III* (Scheme 1) proceeds stereospecifically also on the benzylic carbon atom. We can justifiably assume that it will proceed stereospecifically also on such carbon atoms which form less stable carbonium ions and that the reaction of 2-chloroethyl isothiocyanates with nucleophiles is suitable for preparation of stereoisomerically pure 4,5-disubstituted Δ^2-1,3-thiazolines or thiazolidine-2-thiones.

Assignment of Configuration

The stereospecific course of reactions of diastereoisomers *XI* and *XII* with nucleophilic reagents proves that the cyclization is an intramolecular S_N2 substitution of chlorine. This means that the *threo*-isomer is converted into cyclic products of *cis*-configuration whereas the *erythro*-isomer affords *trans*-isomers. We assigned provisionally *threo*- and *erythro*-configuration to compounds *XI* and *XII* respectively from correlation with compounds *IX* and *X* (thiophosgene reacts only with the amino group and does not affect configuration of the asymmetric carbon atom). However, configuration of the starting diastereoisomers *IX* and *X*, derived from coupling constants of vicinal protons alone, without data on conformational population, may not necessarily be correct. It was therefore advisable to determine configuration of the heterocyclic products *XIII*–*XX* which would in turn afford information about configuration of the isothiocyanates *XI* and *XII*.

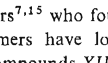
It is generally accepted that in five-membered heterocycles the coupling constant between two *cis*-placed vicinal methine protons is larger than for the *trans*-arrangement[7,12,13]. This holds, of course, strictly only for planar systems; for non-planar, conformationally mobile, systems (such as *e.g.* compounds *XIII*–*XX*) this assumption may not be correct. The coupling constants $^3J(H_A, H_B)$, given in Table I, demonstrate the ambiguity of such configurational assignment. Although the isomers *XIII*

and *XIX*, to which we assigned *cis*-configuration, have indeed larger vicinal coupling constants than the corresponding *trans*-isomers *XIV* and *XX*, compounds *XV* and *XVII* which must possess the same configuration as *XIII* and *XIX* exhibit smaller coupling constants than the *trans*-isomers *XVI* and *XVIII*. For this reason we assigned configuration on the basis of other ^{1}H-NMR spectral data.

In the ^{1}H-NMR spectra, the phenyl group should exert a greater shielding effect on a nearer (*cis*) vicinal group, *i.e.* either on the CH_3 group or on the H_B proton; this should result in an upfield shift of the corresponding signal. It is clearly seen from Table I that the methyl signals (δ_{CH_3}) in isomers *XIII*, *XV*, *XVII* and *XIX* are shifted upfield relative to those of the compounds *XIV*, *XVI*, *XVIII* and *XX*; this indicates that in the first series of isomers the phenyl and methyl groups are in a *cis*-relation. An opposite trend is observed for signal of the proton H_B, indicating thus a *cis*-relation of phenyl and the H_B proton in compounds *XIV*, *XVI*, *XVIII* and *XX*. This configurational assignment also agrees with values of coupling constants between methyl protons and the H_B proton, $^3J(CH_3, H_B)$, which, according to Samek[14], should be larger for *cis*- than for *trans*-isomers. Our conclusions are in accord also with studies of Foglia and coworkers[7,15] who found that in series of isomeric oxazolines[15] and thiazolines[7] *cis*-isomers have longer gas–liquid chromatographic retention times. In our study, the compounds *XIII* and *XXI*, assigned *cis*-configuration, exhibit longer retention times than the *trans*-isomers *XIV* and *XXII*.

TABLE I

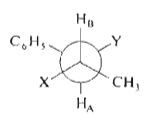
^{1}H-NMR Spectral Characteristics of Grouping



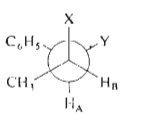
in Heterocyclic Compounds *XIII*—*XX*

Compound	δ_{CH_3}	δ_{H_B}	$^3J(H_A, H_B)$	$^3J(CH_3, H_B)$	NOE (%)	
					$f_{(H_A(CH_3))}$	$f_{(H_B(CH_3))}$
XIII	0·95	4·51	7·5	6·85	1	11
XIV	1·35	4·31	7·0	6·55	7	10
XV	1·02	4·66	7·4	6·65	1	10
XVI	1·40	4·35	8·75	6·35	8	10
XVII	0·91	4·33	6·55	6·55	1	15
XVIII	1·22	4·08	8·6	6·20	8	15
XIX	0·97	4·5	7·1	6·70	1	11
XX	1·30	4·33	6·3	6·35	9	11

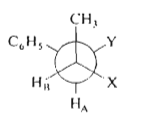
Configuration of the studied compounds has been unequivocally proved by the nuclear Overhauser effect (NOE). Under assumption that dipole–dipole relaxation mechanism contributes decisively to relaxation of the studied protons, the observed NOE contributions for the given proton are indirectly proportional to the sixth root of the distance from the particular saturated proton. Molecular models of compounds *XIII*–*XX* show that the distance between the methyl group and the hydrogen H_B is constant for the whole series ($r(H_B, CH_3) = 0{\cdot}25$ nm, for CH_3 the distance is measured from the center of the circle, made by the rotating hydrogens) whereas the distance between the methyl group and the H_A hydrogen depends on relative configuration of the compound. Irrespective of exact conformation of the heterocycle, the distance $r(H_A, CH_3)$ must be greater in *cis*-isomers (about 0·32–0·37 nm) than in *trans*-isomers (about 0·26–0·28 nm). In accord with the findings of Nakanishi and coworkers[16] we can therefore expect that saturation of the methyl group should be accompanied by a marked NOE at H_A only for *trans*-isomers whereas



XXIIIa

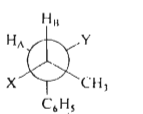


XXIIIb

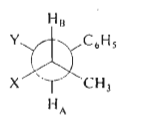


XXIIIc

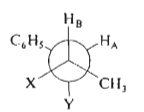
erythro



XXIVa



XXIVb



XXIVc

threo

for *cis*-isomers the effect, if any, should be very small. We found (Table I) that saturation of the methyl group resulted in 7–9% NOE at H_A for compounds *XIV*, *XVI*, *XVIII* and *XX* whereas for other studied compounds the effect was almost zero (1%). Under the same conditions, we observed for the whole series a 10–15% NOE at the H_B proton.

The obtained results prove that compounds *XIII*, *XV*, *XVII* and *XIX* have *cis*-configuration whereas compounds *XIV*, *XVI*, *XVIII* and *XX* have *trans*-configuration. The relatively large coupling constants $^3J(H_A, H_B)$ (6·3–8·75 Hz) in the *trans*-isomers indicate that they exist predominantly in a conformation with the phenyl and methyl groups in equatorial positions. Since the diastereoisomer *XI* is transformed into

heterocyclic derivatives of *cis*-configuration, it must have *threo*-configuration and thus the compound *XII* must be the *erythro*-isomer. This confirms the previous configurational assignment to the starting amines *IX* and *X*.

Conformational Analysis

After configuration has been assigned to the diastereoisomeric isothiocyanates *XI* and *XII*, some conclusions about conformational population in these compounds can be made on the basis of the vicinal coupling constants $^3J(H_A, H_B)$. These constants can be compared with those of analogous vicinal halides or pseudohalides of the type *XXIII* and *XXIV*, *e.g.* dithiocyanates[17] (X=Y=SCN), dibromides[18] (X=Y=Br) or dichlorides[19] (X=Y=Cl). Conformers with vicinal antiperiplanar methine protons H_A and H_B (*XXIIIa*, *XXIVb*) should exhibit in ^{1}H-NMR spectrum a coupling constant of about 10–12 Hz whereas constants corresponding to other conformers with synclinal relation of these protons should amount to only 1–3 Hz.

Considering only steric repulsive interactions between substituents, the most stable conformation of the *erythro*-isomer *XXIII* should be the antiperiplanar form *XXIIIa*. The vicinal coupling constants in Table II indicate that conformer *XXIIIa* predominates in the 1,2-dithiocyanato (X=Y=SCN) and 1,2-dibromo (X=Y=Br) derivatives but its proportion drops in the 1,2-dichloro derivative (X=Y=Cl) and is lowest in the isothiocyanate *XII* (*i.e. XXIII*; X=NCS and Y=Cl). This fact indicates that whereas in the 1,2-dithiocyanato and 1,2-dibromo derivatives steric repulsive interactions between the SCN groups or Br atoms are the dominant factor, in the chloroisothiocyanate *XII* an electronic attractive interaction between substituents NCS and Cl operates, stabilizing thus conformers *XXIIIb* and *XXIIIc*.

Further, we see from Table II that for the considered *threo*-isomer *XXIV* the conformer *XXIVb* predominates only in the dithiocyanato derivative whereas

TABLE II

Vicinal Coupling Constants, $^3J(H_A, H_B)$, in 1,2-X,Y-Disubstituted 1-Phenylpropanes *XXIII* and *XIV*

X	Y	*XXIII*	*XIV*
—SCN	—SCN	10·2*ε*	9·0*ε*
—Br	—Br	11·0[a]	5·5[a]
—Cl	—Cl	8·0*ε*	5·7*ε*
—NCS	—Cl	6·4[b]	5·8[b]

ε Data from reference[17]; [b] measured at 80 MHz in tetrachloromethane (internal standard tetramethylsilane).

in all other compounds, including the chloroisothiocyanate *XI* (*XXIV*; X=NCS, Y=Cl), conformers *XXIVa* and *XXIVc* constitute the main portion of the conformation mixture. Also in this case, analogically to the *erythro*-isomer *XII*, we could assume attractive interactions between the chlorine atom and the NCS group in the *threo*-isomer *XI*, resulting in predominant population of the conformer *XXIVc*.

EXPERIMENTAL

Melting points of the synthesized compounds were measured on a Kofler block and are uncorrected. IR spectra were taken in chloroform on a double beam spectrophotometer UR—20 (Zeiss, Jena). The ^{1}H-NMR spectra of the open-chain compounds *IX*—*XII* were measured on a Tesla BS—487 80 MHz instrument, those of the heterocyclic derivatives *XIII*—*XX* (as well as the Overhauser effects) on a Varian XL—200 pulse FT-NMR spectrometer (200 MHz) in deuteriochloroform with tetramethylsilane as internal standard. Gas–liquid chromatographic analyses were performed on a Carlo Erba Fractovap 2200 V chromatograph.

erythro-1-Phenyl-1-hydroxy-2-propylammonium Chloride (*IV*)

A mixture of *erythro*- and *threo*-2-amino-1-phenylpropan-1-ol (7·1 g; prepared according to ref.[9]) was crystallized four times from an ethanol–ethyl acetate mixture, yielding 4·5 g (63%) of pure product *IV*, m.p. 194—196°C (reported[9] m.p. 192°C).

trans-2,5-Diphenyl-4-methyl-1,3-oxazoline (*VI*)

Benzoyl chloride (9·5 ml; 82·6 mmol) in chloroform (36 ml) was added dropwise to a stirred and cooled mixture of the *erythro*-isomer *IV* (15 g; 79·9 mmol), chloroform (78 ml) and a 25% aqueous sodium hydroxide solution (38 ml). The precipitate was filtered, washed with light petroleum and crystallized from ethanol, affording 19·6 g (96%) of erythro-2-benzoylamino--1-phenylpropan-1-ol (*V*), m.p. 146—147°C (reported[20] m.p. 144°C). A solution of this product in thionyl chloride (45 ml) was stirred for 1 h at room temperature and thionyl chloride was taken *in vacuo*. The residue was decomposed with water under cooling and the solution made alkaline with a saturated aqueous sodium carbonate solution. The precipitated solid was collected on filter, washed with chloroform and crystallized from ethanol, yielding 7·8 g (35%) of *threo*-1-benzoyloxy-1-phenyl-2-propylammonium chloride (*VII*), melting at 218—220°C (reported[20] m.p. 220°C).

The filtrate was extracted with chloroform, the extract dried over sodium sulfate and taken down. Distillation of the residue afforded 8·2 g (45%) of the *trans*-isomer *VI*, b.p. 138°C/78·5 Pa. For $C_{16}H_{16}NO_2$ (237·3) calculated: 80·99% C, 6·37% H, 5·90% N; found: 81·05% C, 6·70% H, 5·71% N. IR spectrum ($CHCl_3$): ν(C=N) 1 648 cm^{-1}. ^{1}H-NMR spectrum (CCl_4): 7·25—7·94 (m, C_6H_5 and N—C_6H_5), 4·94 (d, —CH—), 4·06 (m, —CH—), 1·4 (d, CH_3).

threo-1-Phenyl-1-hydroxy-2-propylammonium Chloride (*VIII*)

A solution of the *trans*-isomer *VI* (8·2 g; 34·6 mmol) in dilute (1:1) HCl (225 ml) was refluxed for 30 h, filtered with charcoal and taken down. Crystallization of the residue from ethyl acetate gave 4·8 g (74%) of the *threo*-isomer *VIII*, m.p. 173—174°C (reported[9] m.p. 169°C). The compound *VIII* was obtained in the same manner and yield also by hydrolysis of *threo*-1-benzoyloxy-1-phenyl-2-propylammonium chloride (*VII*).

threo-1-Chloro-1-phenyl-2-propylammonium Chloride (*IX*)

Thionyl chloride (9·5 ml; 128 mmol) was added dropwise to a stirred suspension of the chloride *IV* (12 g; 64 mmol) in benzene (40 ml), the stirring was continued for 14 h at room temperature and the mixture was taken down. The residue contained, according to ^{1}H-NMR spectrum, only one diastereoisomer. Crystallization from ethanol afforded 10·8 g (82·4%) of the pure *threo*-isomer *IX*, m.p. 212—213°C. For $C_9H_{13}Cl_2N$ (206·1) calculated: 52·45% C, 6·35% H, 6·80% N; found: 52·80% C, 6·71% H, 6·63% N. ^{1}H-NMR spectrum (^2H_2O): 7·75 (C_6H_5), 5·36 (d, —CH—, $J(H_A, H_B) = 9·2$ Hz), 4·25 (m, —CH—), 1·45 (d, CH_3).

threo and *erythro*-1-Chloro-1-phenyl-2-propylammonium Chloride (*IX* + *X*)

A) Reaction with $SOCl_2$: The *threo*-isomer *VIII* (8·8 g) was treated with thionyl chloride as described in the preceding experiment, affording 7·9 g (82·6%) of a mixture of diastereoisomers (*threo* : *erythro* = 2·15 : 1, as determined by ^{1}H-NMR spectroscopy). Addition of pyridine to the reaction mixture in the ratio 0·1 mol of pyridine: 1 mol of the starting *threo*-amino alcohol changed the *threo* : *erythro* ratio in the product to 1·85 : 1. If 1 mol of pyridine was used per 1 mol of the starting amino alcohol, the product ratio was 1 : 1·15.

B) Reaction with PCl_5: A mixture of compound *VIII* (0·33 g; 1·6 mmol), phosphorus oxychloride (1·5 ml) and phosphorus pentachloride (0·33 g; 1·6 mmol) was heated to 115°C for 2 h and then taken down *in vacuo*. The residue was dissolved in water, the aqueous solution made alkaline with conc. sodium hydroxide solution (cooling with ice) and extracted with ethyl acetate. The organic extract was shaken three times with dilute (1 : 10) hydrochloric acid and the aqueous layer was taken down, affording 0·24 g (72·4%) of a mixture of diastereoisomers (*threo* : *erythro* = = 1·25 : 1).

C) Reaction with PCl_3: Phosphorus trichloride (9·4 ml; 106 mmol) was added dropwise to a stirred suspension of the compound *VIII* (4 g; 21·3 mmol) in chloroform (20 ml). The mixture was kept at 50°C for 3 h. After standing overnight at room temperature, the mixture was taken down, the residue dissolved in water and worked up as described under *B*). Yield 3·25 g (75%) of a mixture of *IX* and *X* (1 : 4). Crystallization of this mixture successively from ethanol, ethyl acetate and acetone afforded 0·5 g of pure *erythro*-isomer *X*, m.p. 173—174·5°C. For $C_9H_{13}Cl_2N$ (206·1) calculated: 52·45% C, 6·35% H, 6·80% N; found: 52·62% C, 6·55% H, 6·70% N. ^{1}H-NMR spectrum (^2H_2O): 7·79 (C_6H_5), 5·66 (d, —CH—, $J(H_A, H_B) = 5·2$ Hz), 4·21 (m, —CH—), 1·36 (d, CH_3).

threo-1-Chloro-1-phenyl-2-isothiocyanatopropane (*XI*)

A solution of thiophosgene (4·4 ml; 53·9 mmol) in chloroform (35 ml) was added to a saturated aqueous solution of *threo*-isomer *IX* (3·7 g; 18 mmol). A saturated aqueous solution of sodium carbonate was added dropwise with stirring until the mixture became alkaline. The chloroform layer was separated, dried over calcium chloride and taken to dryness. The product *XI* was distilled, b.p. 103—104°C/129·3 Pa; yield 3·64 g (96%). For $C_{10}H_{10}ClNS$ (211·7) calculated: 56·83% C, 4·76% H, 6·62% N, 15·15% S; found 56·86% C, 4·77% H, 7·41% N, 14·85% S. IR spectrum ($CHCl_3$): ν(NCS) 2101, 2274 cm^{-1}; ^{1}H-NMR spectrum (CCl_4): 7·33 (C_6H_5), 4·79 (d, —CH—, $J(H_A, H_B) = 5·84$ Hz), 4·09 (m, —CH—), 1·34 (d, CH_3, $J(CH_3, H_B) = 6·7$ Hz).

erythro-1-Chloro-1-phenyl-2-isothiocyanatopropane (*XII*)

A mixture of diastereoisomers *IX* and *X* (4 : 1; 2·3 g), obtained by reaction of *VIII* with phosphorus trichloride, was treated as described in the previous experiment, affording 2 g (84%) of a mixture of *erythro*- and *threo*-1-chloro-1-phenyl-2-isothiocyanatopropane *XII* and *XI* in the ratio 4 : 1 (determined by gas–liquid chromatography; 6% DEGS on Chromosorb W-AW-HMDS). Chromatography of this mixture on a column of silica gel (600 g, eluant heptane–ethyl acetate 5 : 1) afforded 1·2 g of the pure *erythro*-isomer *XII*, b.p. 102—104°C/129·3 Pa. For $C_{10}H_{10}ClNS$ (211·7) calculated: 56·83% C, 4·76% H, 6·62% N, 15·15% S; found: 56·86% C, 4·76% H, 7·13% N, 14·85% S. IR spectrum ($CHCl_3$): ν(NCS) = 2100, 2278 cm^{-1}; ^{1}H-NMR spectrum (CCl_4): 7·32 (C_6H_5), 4·79 (d, —CH—, $J(H_A, H_B)$ = 6·38 Hz), 4·08 (m, —CH—), 1·46 (d, CH_3, $J(CH_3, H_B)$ = 6·49 Hz).

cis-5-Phenyl-2-methoxy-4-methyl-1,3-thiazoline (*XIII*)

A solution of the *threo*-isomer *XI* (0·7 g; 3·3 mmol) in methanol (1 ml) was added to a stirred solution of sodium methoxide in methanol (3 ml of 2·6M solution). After standing overnight at room temperature, the mixture was diluted with water (50 ml) and extracted three times with ether. The combined ethereal layers were dried over sodium sulfate and taken down. Gas–liquid chromatographic analysis (15% Apiezon L on Chromaton N-AW-DMS) showed that the product was free of the *trans*-isomer. The residue was chromatographed on a silica gel column (300 g, ether–light petroleum 2 : 1), affording 300 mg (44%) of pure *XIII*, b.p. 98—103°C/51 Pa. For $C_{11}H_{13}NOS$ (207·3) calculated: 63·74% C, 6·32% H, 6·76% N; found: 63·94% C, 6·30% H, 6·70% N. IR spectrum ($CHCl_3$): ν(C=N) = 1629 cm^{-1}, ν(CH_3—O) = 1455, 1107, 1088 cm^{-1}. ^{1}H-NMR spectrum: 7·20—7·50 (C_6H_5), 5·10 (d, —CH_A—, $J(H_A, H_B)$ = 7·55 Hz), 4·51 (m, —CH_B—), 3·96 (s, OCH_3), 0·95 (d, CH_3, $J(CH_3, H_B)$ = 6·95 Hz).

trans-5-Phenyl-2-methoxy-4-methyl-1,3-thiazoline (*XIV*)

Similarly as described in the preceding experiment, the *erythro*-isomer *XII* (500 mg) afforded the compound *XIV* (300 mg; 69%), b.p. 95—100°C/51 Pa; pure according to gas–liquid chromatography. For $C_{11}H_{13}NOS$ (207·3) calculated: 63·14% C, 6·32% H, 6·76% N; found: 63·85% C, 6·15% H, 6·53% N. IR spectrum ($CHCl_3$): ν(C=N) = 1631 cm^{-1}, ν(CH_3—O) = 1451, 1115, 1097 cm^{-1}. ^{1}H-NMR spectrum: 7·25—7·43 (C_6H_5), 4·65 (d, —CH_A—, $J(H_A, H_B)$ = 7 Hz), 4·31 (m, —CH_B—), 3·95 (s, OCH_3), 1·35 (d, CH_3, $J(CH_3, H_B)$ = 6·55 Hz).

cis-5-Phenyl-4-methyl-1,3-thiazolidine-2-thione (*XV*)

A solution of the *threo*-isomer *XI* (0·5 g) in methanol (1 ml) was added to a stirred 10% methanolic solution (2·5 ml) of NaHS. After 30 min, the mixture was acidified with dilute (1 : 1) HCl, diluted with water (50 ml) and extracted with chloroform. The organic layer was dried and taken down leaving 0·5 g of a crude residue, m.p. 130—134°C, which did not exhibit any signals of the *trans*-isomer *XVI* in the ^{1}H-NMR spectrum (Varian XL-200). A sample (0·2 g) of this product on treatment with dimethyl sulfate[7] gave *cis*-5-phenyl-4-methyl-2-methylthio-1,3-thiazoline (*XXI*) which, as shown by gas–liquid chromatography (15% Apiezon L on Chromaton N-AW-DMCS) was free of the *trans*-isomer. Crystallization of the crude residue from chloroform afforded pure *XV*, 133—134·5°C. For $C_{11}H_{11}NS_2$ (221·3) calculated: 57·38% C, 5·30% H, 6·70% N; found: 56·87% C, 5·14% H, 6·32% N. IR spectrum ($CHCl_3$): ν(NH) = 3400 cm^{-1}, ν(CSNH) = = 1478 cm^{-1}. ^{1}H-NMR spectrum: 8·30 (NH), 7·27—7·43 (m, C_6H_5), 4·97 (d, —CH_A—, $J(H_A, H_B)$ = 7·4 Hz), 4·66 (m, —CH_B—), 1·02 (d, CH_3, $J(CH_3, H_B)$ = 6·5 Hz).

trans-5-Phenyl-4-methyl-1,3-thiazolidine-2-thione (*XVI*)

By the same procedure as described in the preceding experiment, the *erythro*-isomer *XII* (0·5 g) was converted into the crude product, m.p. 75—80°C (0·5 g), which, according to its ^{1}H-NMR spectrum and gas–liquid chromatographic analysis of its S-methyl derivative *XXII*, did not contain any *cis*-isomer. Crystallization from tetrachloromethane gave pure *XVI*, m.p. 80—82°C, in 90% yield. For $C_{11}H_{11}NS_2$ (221·3) calculated: 57·38% C, 5·30% H, 6·70% N; found: 57·30% C, 5·10% H, 6·32% N. IR spectrum ($CHCl_3$): ν(NH) = 3401 cm^{-1}, ν(CSNH) = 1473 cm^{-1}. ^{1}H-NMR spectrum: 7·93 (NH), 7·32—7·46 (C_6H_5), 4·73 (d, —CH_A—, $J(H_A, H_B)$ = 8·75 Hz), 4·35 (m, —CH_B—), 1·40 (d, CH_3, $J(CH_3, H_B)$ = 6·35 Hz).

cis-5-Phenyl-2-phenylamino-4-methyl-1,3-thiazoline (*XVII*)

Aniline (0·21 g; 2·27 mmol) was added to a solution of *threo*-isomer *XI* (0·4 g; 1·89 mmol) in ether (1 ml) and the mixture was set aside overnight at room temperature. The solvent was evaporated, the residue dissolved in methanol (3 ml) and the solution adjusted to pH 12 with saturated methanolic solution of NaOH. After 30 min the mixture was diluted with water (20 ml) and the precipitate, m.p. 130—138°C, collected on filter (0·5 g). ^{1}H-NMR spectrum of this product did not exhibit any signals of the *trans*-isomer. Crystallization from aqueous methanol afforded 0·42 g (84%) of pure *XVII*, m.p. 143—144°C. For $C_{16}H_{16}N_2S$ (268·4) calculated: 71·61% C, 6·00% H, 10·44% N; found: 71·98% C, 6·36% H, 10·79% N. IR spectrum ($CHCl_3$): ν(NH) = 3453 cm^{-1}, ν(C=N) = 1638 cm^{-1}; ^{1}H-NMR spectrum: 6·99—7·37 (m, C_6H_5 and N—C_6H_5), 4·75 (d, —CH_A—, $J(H_A, H_B)$ = 6·55 Hz), 4·33 (m, —CH_B—), 0·91 (d, CH_3, $J(CH_3, H_B)$ = 6·55 Hz).

trans-5-Phenyl-2-phenylamino-4-methyl-1,3-thiazoline (*XVIII*)

The *erythro*-isomer *XII* (0·4 g) was converted into pure *XVIII* (400 mg; 79%), m.p. 129—130°C (methanol), similarly as described in the preceding experiment. The crude product was free of the *cis*-isomer (^{1}H-NMR spectrum). For $C_{16}H_{16}N_2S$ (268·4) calculated: 71·61% C, 6·00% H, 10·44% N; found: 71·45% C, 6·28% H, 10·32% N. IR spectrum ($CHCl_3$): ν(NH) = 3416 cm^{-1}, ν(C=N) = 1639 cm^{-1}. ^{1}H-NMR spectrum: 6·98—7·44 (m, C_6H_5 and N—C_6H_5), 4·41 (d, —CH_A—, $J(H_A, H_B)$ = 8·6 Hz), 4·08 (m, —CH_B—), 1·22 (d, CH_3, $J(CH_3, H_B)$ = 6·2 Hz).

cis-2-Diethylamino-5-phenyl-4-methyl-1,3-thiazoline (*XIX*)

Diethylamine (0·3 ml; 2·83 mmol) was added dropwise to an ice-cooled solution of the *threo*-isomer *XI* (0·5 g; 2·36 mmol) in ether (1·5 ml) and the mixture was kept at room temperature overnight. After evaporation of ether the residue was dissolved in methanol (1 ml) and the solution was adjusted to pH 13 by dropwise addition of a saturated methanolic solution of NaOH. The mixture was filtered, the filtrate taken down and distilled, yielding 500 mg (85%) of *XIX*, b.p. 113—115°C/126 Pa. As shown by ^{1}H-NMR spectroscopy, the product was free of the *trans*-isomer. For $C_{14}H_{20}N_2S$ (248·4) calculated: 67·70% 8·11% H, 11·28% N; found: 67·81% C, 8·23% H, 11·05% N. IR spectrum ($CHCl_3$): ν(C=N) = 1600 cm^{-1}. ^{1}H-NMR spectrum: 7·30 (C_6H_5), 4·92 (d, —CH_A—, $J(H_A, H_B)$ = 7·1 Hz), 4·50 (m, —CH_B—), 0·97 (d, CH_3, $J(CH_3, H_B)$ = 6·7 Hz), 3·44 and 1·25 (C_2H_5).

trans-2-Diethylamino-5-phenyl-4-methyl-1,3-thiazoline (*XX*)

Diethylamine (0·6 ml; 5·65 mmol) was added dropwise to an ice-cooled solution of the *erythro*-isomer *XI* (0·5 g; 2·36 mmol) in ether (3 ml) and the mixture was set aside at room temperature

overnight. The separated diethylammonium chloride was filtered off and the filtrate was taken down. The residue (according to ^{1}H-NMR spectrum free of the *cis*-isomer) was distilled at 123 to 125°C/52 Pa, affording 530 mg (90%) of *XX*. For $C_{14}H_{20}N_2S$ (248·4) calculated: 67·70% = 8·11% H, 11·28% N; found: 68·05% C, 8·38% H, 11·14% N. IR spectrum ($CHCl_3$): ν(C=N) = = 1 604 cm^{-1}. ^{1}H-NMR spectrum: 7·24—7·41 (m, C_6H_5), 4·45 (d, —CH_A—, $J(H_A, H_B)$ = = 6·3 Hz), 4·33 (m, —CH_B—), 1·30 (d, CH_3, $J(CH_3, H_B)$ = 6·35 Hz), 3·38 and 1·19 (C_2H_5).

Measurement of Nuclear Overhauser Effect (NOE) in Compounds *XIII—XX*

Solutions in deuteriochloroform of comparable concentrations (about 10 mg of compound in 0·5 ml of solution) were used (dissolved oxygen was not removed). In order to determine the appropriate repetition time between pulses, the following relaxation times T_1 have been determined by the "inversion-recovery" technique: T_1: H_A 2·3 s, H_B 2·0 s, CH_3 0·8 s, C_6H_5 3·0 s, CH_2 0·9 s and CH_3 1·4 s (the last two values for the ethyl group). The measurement of NOE was performed as follows: The spectrum taken without saturation of methyl (RF-pulse (4 μs = = flip angle *c.* 40°) — acquisition (4 s) — delay time (10 s), switched off decoupler) was compared with spectrum obtained under identical conditions but with decoupler switched on for 10 s delay time when the methyl signal was saturated, and NOE at the protons H_A and H_B were observed. Comparison of integrated intensities of the H_A and H_B signals in both spectra afforded the values of NOE which are given in Table I. The amplitude of the irradiation field was adjusted so as to afford the greatest values of NOE.

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