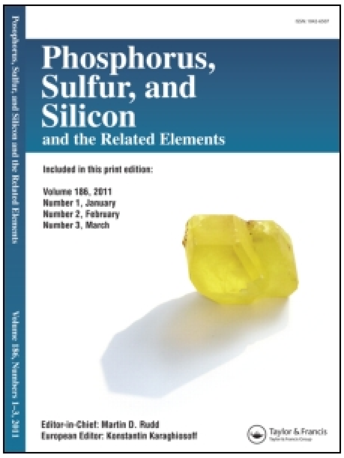

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CONFORMATIONS OF 4,5,6-TRIPHENYL-TETRAHYDRO-1,3-THIAZINE-2-THIONES AND THEIR N-ALKYL DERIVATIVES. UNUSUAL THIAZINETHIONE OR AZETIDINE FORMATION UPON REACTION OF 3-AMINO- AND 3-METHYLAMINO-1,2,3-TRIPHENYLPROPYL CHLORIDES WITH POTASSIUM ETHYLXANTHATE

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Reaction of 3-amino- or 3-methylamino-1,2,3-triphenylpropyl chlorides (**6** or **7**) with potassium ethylxanthate leads to 4,5,6-triphenyl-tetrahydro-1,3-thiazine-2-thione **1** or 1-methyl-2,3,4-triphenylazetidine **8** depending on the N-substitution. Conformational distribution of all possible diastereoisomeric thiazinethiones **1** and their N-alkyl derivatives **2–5** is determined by means of ^{1}H NMR spectroscopy. Allylic strain caused by N- substituents in the *trans,cis*-isomers strongly shifts the equilibrium between conformations with a,a,e or e,e,a phenyl groups towards the conformer with an axial neighbouring Ph-4 group. Vicinal couplings data for the diastereoisomeric azetidine **8** show different ring geometry depending on the configuration.

Keywords: Thiazinethiones; conformations; allylic strain; NMR; chemoselectivity; azetidines

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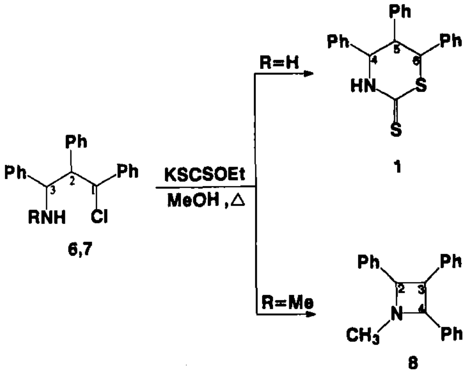
INTRODUCTION

We are interested in conformational behaviour of heterocyclic derivatives, of 1,3-bifunctional diastereoisomers with two or three neighbouring phenyl groups. Steric hindrance of such compounds makes them useful models for conformational relationship studies. In the hitherto reported studies on different isomers of 4,5-diphenyl-[1] and 4,5,6-triphenyl-tetrahydro-1,3-oxazine-2-ones[2] a N-substituent strongly shifted the equilibrium towards the conformation with an axial neighbouring phenyl group as a result of allylic strain[3]. The role of similar effect in sulfur derivatives is not well studied so in this paper we report on the conformational distribution of sulfur analogues of diastereoisomeric triphenylated oxazinones, namely 4,5,6-triphenyltetrahydro-1,3-thiazine-2-thiones (**1**) and their N-alkylated derivatives (**2–5**). We also wish to present the different behaviour of the starting 3-amino- and 3-methylamino-1,2,3-triphenylpropyl chlorides (**6** resp. **7**) in the reaction with potassium ethyl xanthate shown on Scheme 1.



6, R=H	1, %
TT/ET 4.7 : 1	60 *trans,cis*
ET/TT 8.3 : 1	86 *trans,trans*
EE/TE 1.2 : 1	44 *cis,trans* + 22 *cis,cis*
EE/TE 7.5 : 1	83 *cis,trans*

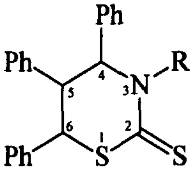
7, R=Me	8, %
TT/ET 6.9 : 1	73 *cis,trans* + 9 *trans,trans*
EE/TE 1.6 : 1	43 *cis,trans* + 28 *cis,cis*

SCHEME 1

RESULTS AND DISCUSSION

Conformations of triphenylated thiazinethiones

The model N-substituted thiazinethiones **2–5** were prepared by alkylation of the corresponding diastereoisomeric compounds **1** with already known configuration[4]. The four possible isomers of the following general Formula are now available:[*]



*cis,cis** - **1-5**
*trans,cis** - **1-5**
*cis,trans** - **1-5**
*trans,trans** - **1, 3**

Compd.	1	2	3	4	5
R	H	CH_3	C_2H_5	$i\text{-}C_3H_7$	allyl

In all compounds the protons of the propane skeleton gave rise to AMX spectra (J_{AM}=0) with H-5 resonance at highest field as a doublet of doublets as can be seen from Table I. The doublets of H-4 are broadened or further split due to coupling to the neighbouring NH proton and this was the criterium for their assignment. The same proton in N-alkyl thiazinethiones shows a similar patern of behaviour. Since H-4 and H-6 protons appeared at nearly the same field, assignment of their signals was checked additionaly by the 2D NMR technique HMQC applied to selected compounds (Table II). The C-4 carbon is shifted downfield due to its bonding with N-atom in comparison with C-6 which is bonded with S-atom. The cross peaks in the ^{1}H-^{13}C correlations (HMQC) confirmed assignment of signals in proton spectra.

The following stereochemical conclusions were reached on the bases of the coupling constants presented on Table I. The diastereoisomers of compounds **1–5** as sofa conformations are shown on Scheme 2. An indication for the ring geometry can be obtained from the coupling constants for the *cis,cis* isomers where the phenyl groups are symmetrically arranged in a single e,a,e-conformation **A**. Almost the same values found for $J_{4,5}$ (3.4–4.3 Hz) and $J_{5,6}$ (4.1–4.3 Hz) reflect the more or less equal torsion angles of the bonds at C-4,5 and C-5,6 which is in accordance with the sofa conformation. On the contrary the alternative half-chair conformation is prefered for the triphenylated tetrahydro-1,3-oxazine-2-ones[2] where for the N-unsubstituted *cis,cis*-isomer $J_{4,5}$ is 4.9–5.0 Hz against a $J_{5,6}$ value of 2.7–2.8 Hz.

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[*] Such designation are used for the sake of simplicity to denote the relative configurations at C-4,5 and C-5,6 respectively according to IUPAC nomenclature, e.g. *trans,cis* refers to the r-4,t-5,t-6-isomer.

TABLE I ^1H NMR data of 4,5,6-triphenyl-tetrahydro-1,3-thiazine-2-thione **1** and their N-alkyl derivatives **2–5**

Compound	*H-4*	*H-5*	*H-6*	J_{45}	J_{56}	*Other*
cis,cis-**1**	5.240 d	3.496 dd	5.333 d	3.4	4.4	NH 8.051
cis,cis-**2**	5.312 d	3.549 dd	5.344 d	4.3	4.2	CH_3 2.633
cis,cis-**3**	5.321 d	3.554 dd	5.365 d	4.1	4.1	CH_2 3.271, CH_3 1.449
cis,cis-**4**	5.285 d	3.527 dd	5.341 d	4.2	4.3	CH (i-Pr) 4.161, 2CH_3 (i-Pr) 1.408, 1.514
cis,cis-**5**	5.411 d	3.592 dd	5.429 d	4.1	4.1	CH_2 3.972, CH 6.028, CH_2= 5.221 (cis, 10.0, 2.1, 1.1), 5.376 (trans, 17.0, 2.7, 1.2)
trans,cis-**1**	4.984 dd	3.790 dd	4.450 d	7.9	3.9	NH 8.321, J_{23} 2.3
trans,cis-**2**	5.397 d	3.428 dd	4.504 d	5.0	3.7	CH_3 2.566
trans,cis-**3**	5.406 d	3.430 dd	4.511 d	4.7	3.6	CH_2 3.193, CH_3 1.389
trans,cis-**4**	5.386 d	3.417 dd	4.493 d	5.0	3.6	CH (i-Pr) 4.050,2CH_3 (i-Pr) 1.401, 1.428
trans,cis-**5**	5.407 d	3.444 dd	4.512 d	5.0	3.7	CH_2 3.871, CH 5.974, CH_2= 5.163 (*cis*, 10.0, 2.2, 1.3), 5.289 (trans, 16.9, 2.7, 1.4)
cis,trans-**1**	4.903 d	4.066 dd	4.745 d	4.0	11.3	NH 8.734
cis,trans-**2**	5.222 d	3.747 dd	4.740 d	4.0	9.8	CH_3 2.498
cis,trans-**3**	5.267 d	3.772 dd	4.763 d	3.4	10.0	CH_2 3.188, CH_3 1.351
cis,trans-**4**	5.203 d	3.738 dd	4.730 d	3.9	9.6	CH (i-Pr) 3.976, 2CH_3 (i-Pr) 1.190, 1.246
cis,trans-**5**	5.258 d	3.768 dd	4.761 d	4.0	10.0	CH_2 3.878, CH 5.924, CH_2= 5.124 (*cis*, 10.0, 2.2, 1.1), 5.280 (trans, 16.9, 2.7, 1.3)
trans,trans-**1**	4.900 d	3.532 dd	4.942 d	10.0	11.3	NH 8.057
trans,trans-**3**	4.855 d	3.156 dd	4.811 d	10.9	11.3	CH_2 2.982, CH_3 1.232

TABLE II ^{13}C NMR data and ^{1}H-^{13}C correlation of 3-alkyl-4,5,6-triphenyl-tetrahydro-1,3-thiazine-2-thiones

Compound	*C-4*	*C-5*	*C-6*	*Other*	*Cross peaks*
cis,cis-**4**	67.160	48.738	52.000	C-2 158.207, CH (i-Pr) 35.742, 2 CH_3 (i-Pr) 23.828, 22.775	5.285/67.160, 3.527/48.738, 5.341/52.000, 4.161/35.742, 1.514/23.828, 1.408/22.775
trans,cis-**5**	65.373	49.644	46.774	C-2 155.207, CH_2 33.108, CH= 133.631, CH_2= 117.818	5.407/65.373, 3.444/49.644, 4.512/46.774, 3.871/33.108, 5.974/133.631, 5.163 and 5.289/117.818
cis,trans-**4**	67.283	49.220	47.069	C-2 157.526, CH(i-Pr) 36.107, 2 CH_3 (i-Pr) 23.512, 22.698	5.203/67.283, 3.738/49.220, 4.730/47.069, 3.976/36.107, 1.246/23.512, 1.190/22.698
trans,trans-**3**	70.264	53.433	51.270	C-2 155.894, CH_2 (Et) 25.094, CH_3(Et) 14.750	4.855/70.264, 3.156/53.433, 4.811/51.270, 2.982/25.094, 1.232/14.750

The *trans,cis*-series of compounds is of particular interest because of the equilibrium between conformers **C** and **D**. In the N-unsubstituted compound **1** the value of 7.9 Hz found for the trans-coupling $J_{4,5}$ shows a preference for the e,e,a- conformer **C**. N-alkylation leads to conformational changes. The low values of 4.7–5.0 Hz observed for $J_{4,5}$ in the trans,cis N-substituted derivatives **2–5**, which are practically substituent independant, indicate an equilibrium shifted to the diaxial conformer **D**. This shift is apparently due to interaction of N-substituent and the vicinal equatorial phenyl as a result of some ring flattening caused by a partial double N-CS bond character. In other words the effect is similar to the familiar allylic strain A-1,2[3].

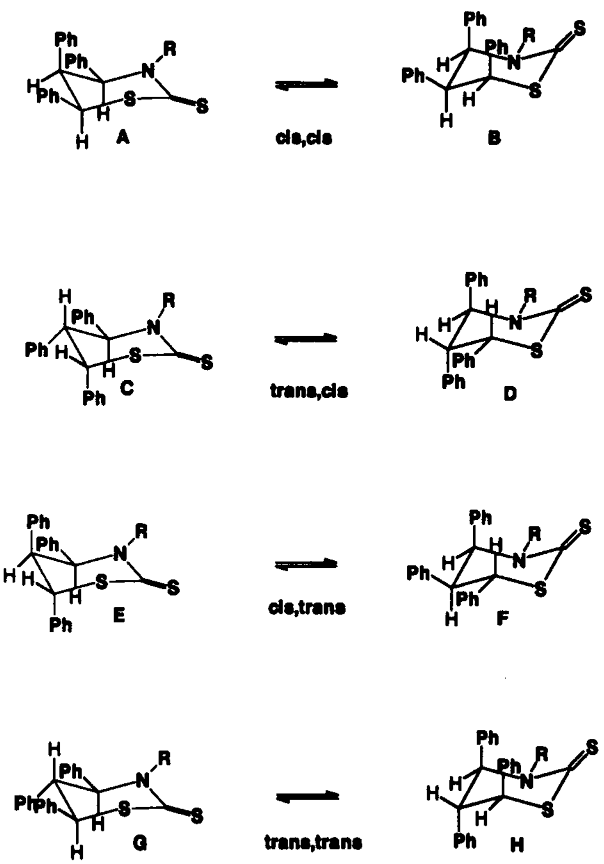
In complete contrast to the case of the *trans,cis*-N-substituted derivatives where a,a,e-conformation is strongly prefered in the *cis,trans*-series of compounds the equilibrium is shifted to the diequatorial conformer **F** as indicated by the J_{56} value of 9.6–11.3 Hz.

The *trans,trans*-isomers **1** and **3** are in the biased triequatorial conformation **G** evidanced by the high J_{45} (10.0–10.9 Hz) and J_{56} (11.3 Hz) values. The alternative a,a,a-conformation **H** can be ruled out on steric grounds as it involves axial phenyl groups in positions 4 and 6.

In conclusion it may be stated that the conformational distribution for the 4,5,6-triphenyl-thiazinethiones **1–5** studied in this work is strongly affected by the N-substituents. The allylic strain induced by the latter leads to strong preference for either a,a,e- or a,e,e-conformation depending on the *trans,cis-* or *cis,trans*-configuration which shows also the balancing role of the third *cis-* phenyl group.

Diastereoisomeric 1-methyl-2,3,4-triphenylazetidines

In a previous work[4] we reported on the three of the four possible isomers of the N-unsubstituted thiazinethione **1** prepared in a reaction of 3-amino-propyl chloride **6** with potassium ethylxanthate as a result of a ring closure of the intermediate O,S-diester of dithiocarbonic acid with elimination of ethanol. Surprisingly, in an extention to the N-methylthiazinethione **2** from 3-methylamino-propyl chloride **7** and potassium ethylxanthate the unexpected diastereoisomeric 1-methyl-2,3,4-triphenylazetidines **8** were obtained in high yields as can be seen on Scheme 1. The difference in the reaction behaviour of amino and methylamino chlorides studied is most probably due to the higher basicity of the



Compd.	Favoured conformation
1-5	A
1	C
2-5	D
1-5	F
1,3	G

SCHEME 2

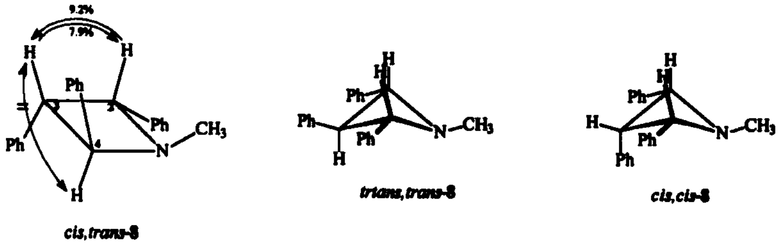
nitrogen in methylamino series where an intramolecular aminolysis is taking place in advance of xanthate formation. Obviously, the potassium ethylxanthate participates in the reaction only as a base but not as a nucleophile. This is demonstrated with the formation of the same products when the reaction is carried out in the absence of potassium ethylxanthate (Na_2CO_3 as a base). On the other hand decrease in a bond angle (3-C-N-H) in methylamino chlorides **7** compared to the amino compounds **6** provoked by the repulsion between the two *gem*-substituents makes the small ring generation more favourable, the co-called Thorpe-Ingold effect[5]. It should be noted however that in the same reaction both amino and methylamino chlorides derived from norephedrine and ephedrine respectively lead to the corresponding 1,3-thiazolidine-2-thiones[6].

The stereochemistry of the azetidines **8** was assigned on the basis of their ^1H NMR spectra (Table III). The common signal for H-2 and H-4 in the *cis,cis-* and *trans,trans-*isomers is a direct proof for their configurations. The vicinal couplings for the third possible isomer *cis,trans-***8** (equal to *trans,cis-***8**) established from NOE experiments (Scheme 3) as J_{trans} 5.4 Hz and J_{cis} 8.7 Hz are in accordance with the data for similar tetrasubstituted azetidines[7]. The different values for J_{trans} of 5.4 and 8.6 Hz and for J_{cis} of 7.8 and 8.6 Hz are an indication for dissimilar ring geometry depending on the configuration. Close values of J_{cis} and J_{trans} in *cis,cis* and *trans,trans* azetidines correlated with puckered conformation according to established data of Kingsbury[8] while in *cis,trans-*isomer the planar ring conformation with dissimilar J_{cis} and J_{trans} values is most likely preferred.

TABLE III ^1H NMR data of 1-Methyl-2,3,4-triphenyl-azetidines **8**

Compound	*H-2*	*H-3*	*H-4*	J_{23}	J_{34}	*Other*
cis,cis-**8**	4.644 d[a]	4.289 tr	4.644 d[a]	7.8	7.8	CH_3 2.652
cis,trans-**8**	5.169 d	4.266 dd	4.897 d	8.7	5.4	CH_3 2.127
trans,trans-**8**	4.077 d[a]	3.397 tr	4.077 d[a]	8.6	8.6	CH_3 2.127
trans,trans-**8** HCl salt	6.023 dd[a]	5.046 tr	6.023 dd[a]	10 9	10.9	NH^+ 13.207, $J_{NH,H-2}$ 6.3, CH_3 1.984, $J_{CH3,NH}$ 5.8

a. Common signal.



cis,trans-8

trans,trans-8

cis,cis-8

SCHEME 3

EXPERIMENTAL

The melting points were taken on capillary tubes; the NMR spectra on a Bruker DRX 250 in deuterochloroform; chemical shifts are quoted in ppm in δ-values, coupling constants in Hz; the mass spectra on a Hewlett Packard GC/MSD 5890/5970 spectrometer.

Reaction of amino chloride 6 and 7 with potassium ethylxanthate. General procedure

To a solution of 3-amino- or 3-methylamino-1,2,3-triphenylpropyl chloride hydrochlorides **6** or **7** (1 mmol) as mixtures of two diastereoisomers with the same configuration at C-2,C-3 in 30 ml of abs. methanol potassium ethylxanthate (3 mmol) was added. After 4 hrs refluxing with stirring the solvent was removed and the residue formed was extracted with methylene chloride-water. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness.

Trans,trans-4,5,6-Triphenyl-tetrahydro-1,3-thiazine-2-thione 1[9]

From ET/TT-3-amino-1,2,3-triphenylpropyl chloride hydrochloride **6** in an isomer ratio of 8.3:1 (NMR); 86% of 1; m.p. 211–2°C (methylene chloride-hexane); Anal. calc for $C_{22}H_{19}NS_2$: C, 73.09; H, 5.30; N, 3.87; S, 17.74. Found C, 73.04; H, 5.24; N, 3.93; S, 17.81.

Cis,cis- and cis,trans-1-Methyl-2,3,4-triphenylazetidine 8

From EE/TE-3-methylamino-1,2,3-triphenylpropyl chloride hydrochloride **7** in an isomer ratio of 1.6:1 (NMR), Column chromatography on Silica gel (ether-hexane 1:5 as eluent): *cis,cis-8*; 43%; m.p. 79–81°C (hexane); MS(EI) 298, 283, 270, 180, 118, 77; Anal. calc for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found C, 88.31; H, 7.09; N, 4.70; *cis,trans-8*, 28%; m.p. 65–7°C (hexane); MS(EI) 298, 283, 270, 180, 118, 77; Anal. calc for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found C, 88.22; H, 7.08; N, 4.65.

Cis,trans- and trans, trans-1-Methyl-2,3,4-triphenylazetidine 8

(a) From TT/ET-3-methylamino-1,2,3-triphenylpropyl chloride hydrochloride **7** in an isomer ratio of 6.9:1 (NMR), Column chromatography on Silica gel (ether-hexane 1:5 as eluent): *cis,trans-8*; 73%, identical with the product obtained from EE/TE-chlorides; *trans,trans-8*; 9%; MS(EI) 298, 283, 270, 180, 118, 77; as hydrochloride: m.p. 188–9°C (benzene-methylene chloride); Anal. calc for $C_{22}H_{22}NCl$: C, 78.67; H, 6.60; N, 4.17. Found C, 78.50; H, 6.76; N 4.33. (b) From the above mixture of methylamino chloride hydrochloride **7** *in the absence of potassium ethylxanthate*, Na_2CO_3 (3 mmol) as a base, Column chromatography on Silica gel (ether-hexane 1:5 as eluent): *cis,trans-8*; 69%; *trans,trans-8*; 6%; both identical with the products according to protocol (a).

N-Alkylation of 4,5,6-triphenyl-tetrahydro-1,3-thiazine-2-thione. General procedure

To a suspension of NaH (3 mmol) (oil was elliminated by trituration with dry pentane) in freshly destillated THF (5 ml) 4,5,6-triphenyltetrahydro-1,3-thiazine-2-thione-**1** (1 mmol) was added. The mixture was stirred at room temperature 0.5 hr and then alkyliodide (8 mmol) was added. After 4 hrs stirring at room temperature NaH was destroyed with water and solvent was removed. The residue formed was extracted with methylene chloride-water. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to give a quantitative yield of the corresponding N-alkyl thiazine thione **2–5**. Analytical data are shown in Table IV.

TABLE IV Analytical data of 3-Alkyl-4,5,6-triphenyl-tetrahydro-1,3-thiazine-2-thiones **2–5**

Compd.	*m.p. (°C)*	*Mol.Form., Mol.Wieght*	*Analysis (found,calc.)*		
			C	*H*	*N*
cis,cis-**2**	141–2	$C_{23}H_{21}NS_2$,	73.38	5.46	3.84
trans,cis-**2**	176–7	375.561	73.35	5.56	3.87
cis,trans-**2**	125–6		73.66	5.50	3.79
		calc:	*73.56*	*5.63*	*3.73*
cis,cis-**3**	110–1	$C_{24}H_{23}NS_2$,	73.75	5.92	3.69

Compd.	*m.p. (°C)*	*Mol.Form., Mol.Wieght*	*Analysis (found,calc.)*		
			C	*H*	*N*
trans,cis-**3**	64–5	389.588	74.06	6.08	3.44
cis,trans-**3**	88–9		74.18	5.99	3.57
trans,trans-**3**	78–9		74.08	6.02	3.56
		calc:	*73.99*	*5.95*	*3.60*
cis,cis-**4**	125–6	$C_{25}H_{25}NS_2$,	74.36	6.19	3.45
trans,cis-**4**	oil	403.615	74.28	6.20	3.60
cis,trans-**4**	89–90		74.32	6.28	3.52
		calc:	*74.40*	*6.24*	*3.47*
cis,cis-**5**	102–3	$C_{25}H_{23}NS_2$,	74.70	5.77	3.49
trans,cis-**5**	oil	401.599	74.69	5.72	3.40
cis,trans-**5**	92–3		74.85	6.04	3.55
		calc:	*74.77*	*5.77*	*3.49*

Acknowledgements

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