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Synthesis and NMR Studies of Chiral 4-Oxazolidinones and Rhodanines

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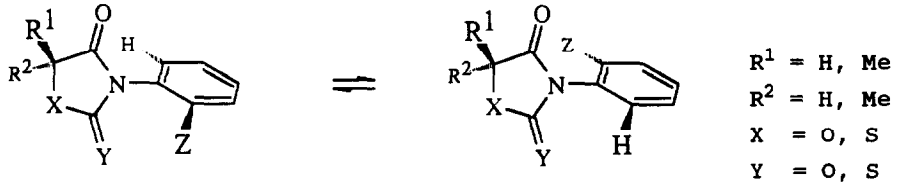
Abstract: Sterically hindered *N*-(o-tolyl) and *N*-(o-chlorophenyl) substituted 2-thioxo-4-oxazolidinones **1** and-thiazolidinones (rhodanines) **2** forming enantiomers by partial rotation around the C-N bond are synthesized. Their chirality is proven by the presence of diastereotopic protons (or carbon atoms) detected by ^{1}H or ^{13}C NMR (**1c**, **2c**). In the presence of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol as an auxiliary the enantiomers showed ^{1}H shift differences of 0.01 ppm for otherwise isochronous nuclei.

INTRODUCTION

Some classes of *N*-aryl heterocycles have been studied in the past with reference to their stereostructures[1-6] which are analogous to the well known case of biaryls. Among those heterocycles, two particular classes were especially attractive to us: 2-thioxo-4-oxazolidinones (*A*, *B*, and *C*; X = O, Y = S) and 2-thioxo-4-thiazolidinones (rhodanines) (X = Y = S). The reasons for this were their barriers to partial rotation around the C-N bond. These seemed to be high enough for preparative separations of stereoisomers.[7] R^1 in



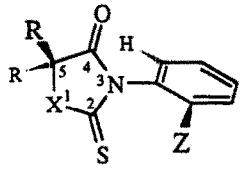
R^1 = H, Me
R^2 = H, Me
X = O, S
Y = O, S
Z = Me, Cl

$R^1 \neq R^2$	*A*	*B*
$R^1 = R^2$	(*M*)-*C*	(*P*)-*C*

diastereomer *A* and R^1 in *B* may exhibit unequal shifts, the same being true for R^2. Indeed, unequal ^{1}H and ^{13}C shifts were shown[1,3] to be present for the groups $R^1 \neq R^2$ in the coexisting diastereoisomers *A* and *B*. The height of the

barrier depends mainly upon the substituent Y. Several 2,4-oxazolidinediones[1] (*A* and *B*; X = Y = O) and 2-thioxo-4-oxazolidinones[3] (X = O, Y = S) were investigated by ^{1}H NMR at 60 MHz by kinetic coalescence of signals at variable temperature, the shift differences of corresponding protons in diastereomers *A* and *B* amounting to $\Delta\delta$ = 0.04 - 0.11 only.

If the groups $R^1 = R^2$, these two fragments may exhibit unequal shifts; in this case, enantiomers (*M*) and (*P*) coexist.[8] In the present work *N-o-aryl* substituted 2-thioxo-4-oxazolidinones **1** and rhodanines **2**, forming enantiomers, are synthesized and their ^{1}H NMR spectra are used for characterization. We report for the first time the unequal shifts of the diastereotopic protons bonded to C-5. In the case of **1c** and **2c**, diastereotopic methyl carbons bonded to C-5 are observed in ^{13}C NMR.



(*M*) and (*P*)

	R	X	Z
1a	H	O	Me
1b	H	O	Cl
1c	Me	O	Me
2a	H	S	Me
2b	H	S	Cl
2c	Me	S	Me

RESULTS AND DISCUSSION

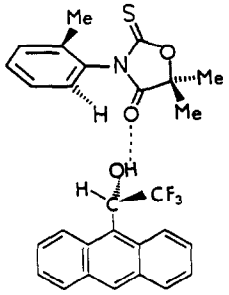
Racemic mixtures of *N*-aryl-2-thioxo-3-oxazolidinones **(±)-1a**, **(±)-1b**, **(±)-1c**, and *N*-aryl-rhodanines **(±)-2a**, **(±)-2b** were synthesized by the reaction of aryl isothiocyanates with α-hydroxy- or α-thiolcarboxylic acid esters. *N*-(o-Tolyl)-5,5-dimethylrhodanine, **(±)-2c**, was prepared by the reaction of ammonium o-tolyldithiocarbamate with α-bromoisobutyric acid potassium salt. In these molecules the C-N bond is a chiral axis and the substituents R on C-5 are diastereotopic.

The 250 MHz ^{1}H NMR spectra of the *N*-(o-chlorophenyl) substituted derivatives **(±)-1b** and **(±)-2b** taken in deuterochloroform showed an AB system for the diastereotopic C-5 ring protons, the shift difference being equal to 0.05 and 0.07 ppm, respectively (Table 1). For the *N*-(o-tolyl) substituted derivatives **(±)-1a** and **(±)-2a** on the other hand diastereotopic protons were not differentiated in deuterochloroform. However, when hexadeuterobenzene was used as solvent, shift differences of 0.08 and 0.05 ppm, respectively, were observed (Figure 1), accompanied with an upfield solvent shift of about 1.4

ppm for both compounds due to the anisotropy effect of the benzene ring. These results are summarized in Table 1. Compounds **(±)-1c** and **(±)-2c** possess diastereotopic methyl groups bonded to C-5 of the heterocyclic ring. These groups exhibited unequal shifts of ^{13}C nuclei, chemical shift differences amounting to 0.8 ppm in hexadeuterobenzene. The ^{13}C NMR chemical shifts of **(±)-1c** and **(±)-2c** are given in Table 2. Only one singlet was observed for the 5-methyl protons of **(±)-1c** and **(±)-2c** both in deuterochloroform and in hexadeuterobenzene, although two singlets might have been possible.

For the heterocyclic compounds studied here, the energy barriers are too high (>100 kJ/mole) to be determined by NMR.[9] Therefore, a different method is applied for these compounds: Enrichment of enantiomers by liquid chromatography on an optically active sorbent and subsequent racemization which will be reported separately.

Optically active auxiliary compounds may be used for determination of enantiomeric purities. It is expected that the auxiliary will associate with each enantiomer and form two diastereomeric and, in principle, NMR distinguishable complexes in solution. The differential shift which will then be produced between the resonances of equivalent nuclei are dependent on the molar ratio of the auxiliary compound and the substrate.



(*M*)-**1c**.....(+)-**3** and (*P*)-**1c**.....(+)-**3**

^1H NMR spectra of **(±)-1a**, **(±)-1b**, **(±)-1c**, and **(±)-2a** were taken in the presence of the auxiliary (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol, **(+)-3**, because it was considered necessary to investigate the behaviour of the racemates in the presence of a chiral auxiliary, in order to be able to make use of it for future enantiomeric purity determinations after enrichment of the enantiomers.[10]

It has been found that, for the 2'-methyl protons, a shift difference of 0.01 ppm was produced between the two components of the racemic mixtures studied (Table 1). For the 5-methylene diastereotopic protons two AB systems

are expected in the presence of **(+)-3**. For **(±)-1a** however, only a single AB set was observed. This means that the shift difference is less than the linewidth in this case. In the absence of **(+)-3** only a singlet was observed for the 5-methylene protons of **(±)-1a**. For *N*-(o-tolyl)-rhodanine, **(±)-2a**, under these conditions, an AB spectrum was observed for the 5-methylene protons for one of the enantiomers, whereas a singlet was observed for the second one (Figure 1). For the *N*-(o-chlorophenyl) derivative **(±)-1b** two AB spectra with shift differences of 0.01 ppm were observed for the 5-methylene protons (Table 1).

Oxazolidinone **(±)-1c** in the presence of eight equivalents of the auxiliary **(+)-3** exhibited the expected two singlets for 2'-CH_3 but only two singlets for 5-CH_3 instead of the possible four singlets (Table 1). All of these signals showed the same intensities which was also true when this solution had been heated to 50°C for 24 h. In principle, unequal intensities[11] could have been expected after establishment of the equilibrium between the two diastereomeric association complexes **(+)-1c.....(+)-3** and **(-)-1c....(+)-3** by rotation about the N-aryl bond.

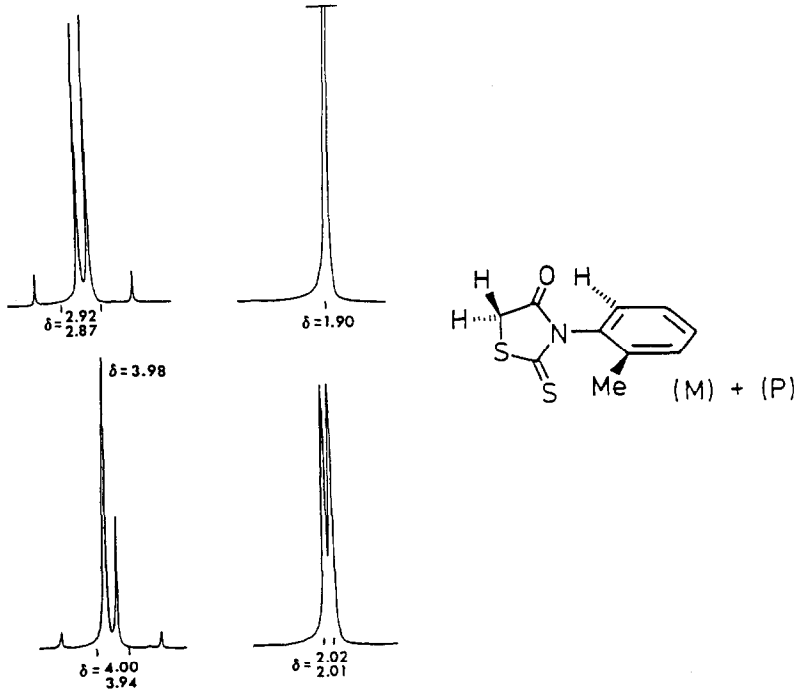
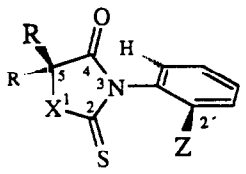
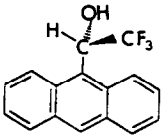


Figure 1. ^1H NMR signals of methylene and methyl protons of **(±)- 2a** at 24°C. Above: in C_6D_6. Below: in $CDCl_3$ in the presence of eight equivalents of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol, **(+)-3**.

Table 1. ^{1}H NMR Data (250 MHz) of the Racemates in the Absence and in the Presence of (*S*)-(+)-1-(9-Anthryl)-2,2,2-trifluoroethanol, **(+)-3**. J_{AB} amounts to 17.0 - 17.2 Hz for **1a/1b** and 18.2 - 18.4 Hz for **2a/2b**.



(*M*) + (*P*)

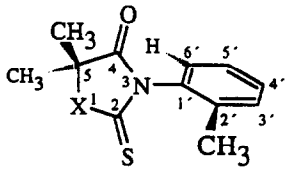


(*S*)-(+)-3

Compound	X	R	Z	Medium	δ (ppm) 5-CH_2	δ (ppm) 2'-CH_3
				C_6D_6	3.67, 3.59 (AB)	1.94
(±)-1a	O	H	CH_3	$CDCl_3$	5.04 (s)	2.21
				[a]	4.87, 4.84 (AB)	2.12
(±)-1b	O	H	Cl	$CDCl_3$	5.09, 5.04 (AB)	-
				[b]	4.87, 4.79 (AB)	-
					4.86, 4.78 (AB)	-
				C_6D_6 [c]	5-CH_3 1.17 (s)	1.96
(±)-1c	O	CH_3	CH_3	$CDCl_3$	5-CH_3 1.75 (s)	2.19
				[a]	5-CH_3 1.55, 1.54	2.04, 2.03
				C_6D_6	2.92, 2.87 (AB)	1.90
(±)-2a	S	H	CH_3	$CDCl_3$	4.22 (s)	2.13
				[a]	4.00, 3.94 (AB)	2.02, 2.01
					3.98 (s)	
(±)-2b	S	H	Cl	$CDCl_3$	4.28, 4.21 (AB)	-
				C_6D_6 [c]	5-CH_3 1.28 (s)	1.94
(±)-2c	S	CH_3	CH_3	$CDCl_3$	5-CH_3 1.81 (s)	2.12

[a] $CDCl_3$, 8 equivalents of (+)-3. [b] $CDCl_3$, 4 equivalents of (+)-3. [c] Spectrum taken at 80 MHz.

Table 2. ^{13}C Chemical Shifts (ppm) of **(±)-1c** and **(±)-2c** in Hexadeuterobenzene.



(*M*) + (*P*)

Compound	**(±)-1c**	**(±)-2c**
X	O	S
2	175.1	178.9
4	188.2	198.4
5	86.1	55.3
5-CH_3	23.4 [a]	27.3 [a]
	22.8 [a]	26.5 [a]
1'	136.2	136.4
2'	132.3	135.2
3'	131.3	131.2
4'	128.8	129.1
5'	130.0	129.8
6'	127.3	127.2
2'-CH_3	17.2	17.1

[a] Diastereotopic groups

EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker WM-250 (250 MHz, T = 24 °C), or on a Bruker AW-80 spectrometer (80 MHz, T = 31°C); ^{13}C NMR spectra were recorded on a Bruker WH-90 spectrometer (22.64 MHz T = 31°C) . UV spectra were obtained in acetonitrile, on a Hitachi U-2000 spectrophotometer. Melting points were determined using Büchi 510 melting point apparatus. Elemental analyses were obtained on a Heraeus CHN-Rapid instrument. (*S*)-(+)-1-(9-Anthryl)-2,2,2-trifluoroethanol, **(+)-3**, was bought from Aldrich.

Starting products. N-(o-Tolyl)-isothiocyanate and N-(o-chlorophenyl)-isothicocyanate were prepared from the corresponding commercially available aniline derivatives and carbon disulfide with lead(II) nitrate, by analogy to lit. 12. Ethyl glycolate was synthesized from glycolic acid (Merck) and abs. ethanol in the presence of chlorosulfonic acid in 25% yield. Ethyl α-hydroxyisobutyrate was purchased from Fluka (purum >97%). Ethyl thioglycolate was bought from Merck.

General procedure for the preparation of N-aryl-2-thioxo-4-oxazolidinones and N-aryl-rhodanines:[2] 0.025 mol of arylisothiocyanate and 0.025 mol of α-

hydroxycarboxylic acid ester or α-thiolcarboxylic acid ester were mixed in 25 ml of toluene. 0.0025 mol of metallic sodium was added in small pieces. The reaction mixture was refluxed for 5 h. Toluene was distilled out and the remaining crude product was purified by recrystallizing twice from ethanol.

N-(o-Tolyl)-2-thioxo-4-oxazolidinone (**(±)-1a**)

Prepared according to the general procedure using ethyl glycolate. ^{1}H NMR ($CDCl_3$): δ= 2.21 (3H, s), δ= 5.04 (2H, s), δ= 7.47 - 7.14 (4H, m). Yield: 22%. M.p. 145°C. Elemental analysis: found C, 58.03; H, 4.32; N, 6.70 calculated for $C_{10}H_9NO_2S$: C, 57.97; H, 4.35; N, 6.76%. UV: λ_{max} (log ε_{max})= 257 nm (4.28), 330 nm (1.70).

N-(o-Chlorophenyl)-2-thioxo-4-oxazolidinone (**(±)-1b**)

Prepared according to the general prodecure using ethyl glycolate. Yield : 25%. M.p. 170-171°C. ^{1}H NMR ($CDCl_3$): δ_A = 5.01, δ_B = 4.96 (2H, AB, J_{AB} = 17.1 Hz), δ= 7.61 - 7.31 (4H, m). Elemental analysis: found C, 47.18; H, 2.71; N, 5.96; Cl, 15.65 calculated for $C_9H_6ClNO_2S$: C, 47.47; H, 2.64; N, 6.15; Cl, 15.60%. UV: λ_{max} (log ε_{max}) = 255 nm (4.24), 328 nm (1.69).

N-(o-Tolyl)-5,5-dimethyl-2-thioxo-4-oxazolidinone(**(±)-1c**)

Prepared according to the general procedure using ethyl α-hydroxyisobutyrate.[3] Yield : 32%. M.p. 97°C.[3]. ^{1}H NMR ($CDCl_3$) : δ= 1.75 (6H, s), δ= 2.19 (3H,s), δ= 7.46 - 7.14 (4H, m). Elemental analysis: found: C, 61.24; H, 5.47; N, 6.00 calculated for $C_{12}H_{13}NO_2S$: C, 61.28; H, 5.53; N, 5.96%. UV: λ_{max}(log ε_{max})= 256 nm (4.23), 332 nm (1.76).

N-(o-Tolyl)-rhodanine(**(±)-2a**)

Prepared according to the general procedure using ethyl thioglycolate. Yield: 42%. M.p. 110°C.[13] ^{1}H NMR ($CDCl_3$) : δ= 2.13 (3H, s), δ= 4.22 (2H, s), δ = 7.45 - 7.05 (4H, m). UV: λ_{max} (log ε_{max}) = 256 nm (4.10), 295 nm (4.15), 388 nm (1.82).

N-(o-Chlorophenyl)-rhodanine (**(±)-2b**)

Prepared according to the general procedure using ethyl thioglycolate. Yield: 40%. M.p. 124°C.[14] ^{1}H NMR ($CDCl_3$) : δ_A = 4.27, δ_B = 4.20 (2H, AB, J_{AB}= 18.2 Hz), δ= 7.60 - 7.22 (4H, m). UV: λ_{max} (log ε_{max}) = 253 nm (4.15), 294 nm (4.16), 386 nm (1.81).

N-(o-Tolyl)-5,5-dimethylrhodanine(**(±)-2c**)

Obtained by the reaction of ammonium o-tolyldithiocarbamate (obtained from carbon disulfide and o-toluidine[12]) with α-bromoisobutyric acid potassium salt. The reaction was carried out in aqu. KOH solution at room temperature. After 0.5 h stirring, the mixture was acidified with HCl and warmed on water bath for 0.5 h. The crude oily product was extracted from the reaction mixture by CCl_4 and purified by recrystallization from ethanol. Yield: 14%. M.p. 72 -73°C. ^{1}H NMR ($CDCl_3$): δ= 1.81 (6H, s), δ= 2.12 (3H, s), δ= 7.41 - 7.07 (4H, m). Elemental analysis: found: C, 57.01; H, 5.15; N, 5.65 calculated for $C_{12}H_{13}NOS_2$:C, 57.34; H, 5.21; N, 5.57%. UV: λ_{max} (log ε_{max})= 257 nm (4.09), 297 nm (4.18), 393 nm (1.80).

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