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Separation and Thermal Racemization of the Enantiomers of Spiro[cyclohexadiene-dihydroacridines]

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Summary. The enantiomers of substituted spiro[cyclohexadiene-dihydroacridines] were separated by enantioselective liquid chromatography with the sorbent/solvent systems triacetylcellulose/methanol, *tris*-(3,5-dimethylphenylcarbamoyl)-cellulose/silica gel (Chiralcel OD^{TM})/*n*-heptane/2-propanol, and (+)-poly-(trityl methacrylate)/silica gel/*n*-heptane/2-propanol. Interconversion barriers of the enantiomers were determined for a series of derivatives by thermal racemization. Electrocyclic ring opening/ring closure in terms of the *Woodward-Hoffmann* rules is discussed for the enantiomerization mechanism; the interconversion of the enantiomers by enolization is ruled out by deuterium exchange experiments.

Keywords. Spiro[cyclohexadiene-dihydroacridines]; Enantiomers; Enantioselective liquid chromatography; Thermal racemization.

Introduction

Some years ago a novel class of photochromic substances [1], the aroylspiro[cyclohexadiene-azaheterocycles], in which an aroylcyclohexadiene moiety is *spiro*-connected with a five- or six-membered nitrogen heterocycle, was discovered [2] and has been intensely studied since that time [3–7]. This type of spiro compounds can easily be synthesized by ring transformation of pyrylium salts with suitable nitrogen heterocycles possessing an integrated enamine structure. Thus, the reaction of 2,4,6-triarylpyrylium salts **1a–h** with the *in situ* generated anhydrobase **3** of the 9,10-dimethylacridinium methylsulfate **2** leads to racemic 6-aroyl-3,5-diaryl-10′-methylspiro[cyclohexa-2,4-diene-1,9′-9′,10′-dihydroacridines] **6a–h** [4]. The N-unsubstituted analogues **6i–l** are obtained from the pyrylium salts **1a**,**f–h** and 9-methylacridine **4** *via* its tautomer **5** [4].

UV-Irradiation of the aroylspiro[cyclohexadiene-dihydroacridines] **6** gives rise to red coloured merocyanines of the type **7** which can be recyclized to the starting spiro compounds **6** photochemically with visible light or by heat [6].

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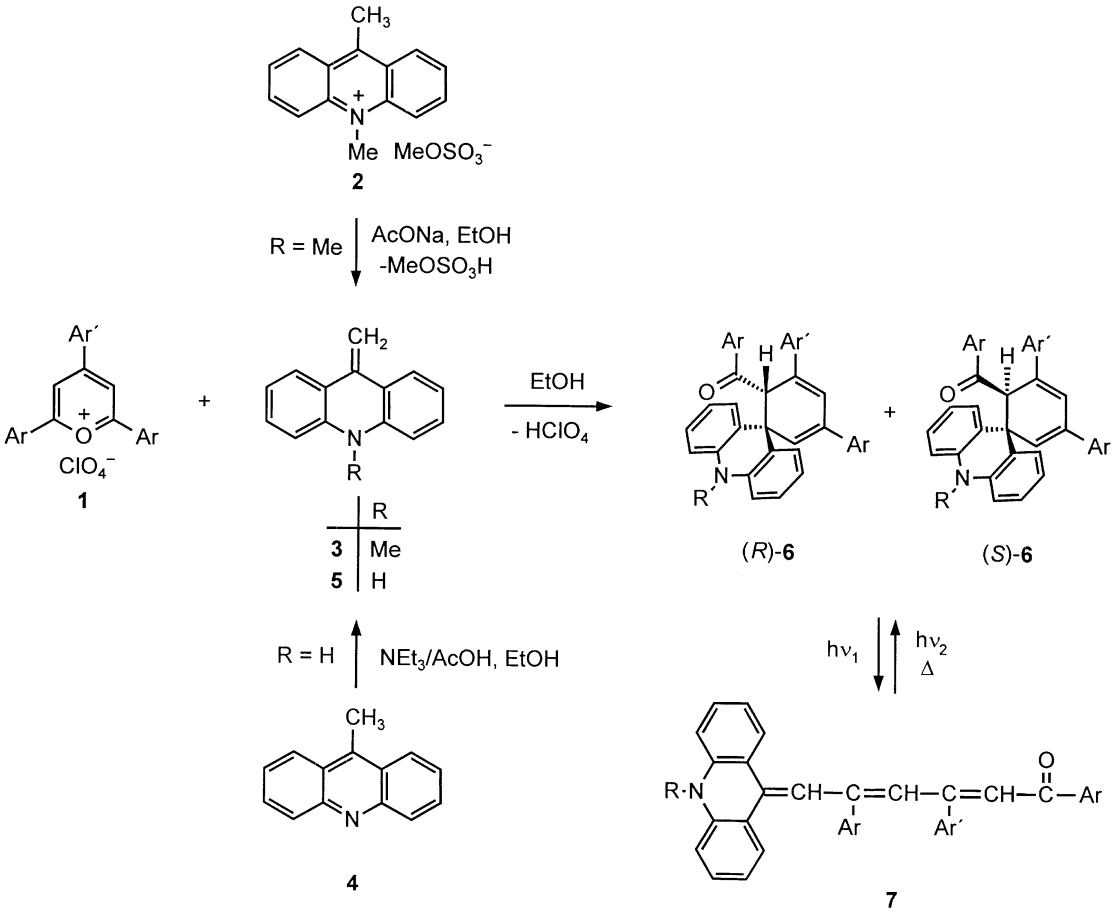


1	Ar	Ar′	*R*	6
a	Ph	Ph	Me	**a**
b	Ph	4-Me-C_6H_4	Me	**b**
c	Ph	4-MeO-C_6H_4	Me	**c**
d	Ph	4-Cl-C_6H_4	Me	**d**
e	Ph	4-Br-C_6H_4	Me	**e**
f	4-Me-C_6H_4	Ph	Me	**f**
g	4-Cl-C_6H_4	Ph	Me	**g**
h	4-Br-C_6H_4	Ph	Me	**h**
a	Ph	Ph	H	**i**
f	4-Me-C_6H_4	Ph	H	**j**
g	4-Cl-C_6H_4	Ph	H	**k**
h	4-Br-C_6H_4	Ph	H	**l**

In the case of racemic aroylspiro[cyclohexadiene-indolines] [7] as well as spiro[indoline-chromenes] and spiro[indoline-benzoxazines] [8], the separation of the enantiomers can be achieved by liquid chromatography on non-racemic stationary phases. The thermal racemization of the enantiomers obtained allows the determination of the free enthalpy of activation $\Delta G^{\neq}$ for the enantiomerization reaction as a valuable parameter for the interpretation of the enantiomerization mechanism. Our continuous interest in the elucidation of such reactions prompted us to extend these studies to the spiro compounds **6** in order to get first insights into the nature of their thermally induced reactions. In this paper we report on the results of such investigations.

Results and Discussions

According to their N-substitution pattern, spiro[cyclohexadiene-dihydroacridines] **6** can be divided into the methyl derivatives **6a–h** and the NH-compounds **6i–l**, representing tertiary and secondary amines, respectively. In both series we prepared examples with electron donating (Me, MeO) or accepting (Cl, Br) substituents in *para*-position of the phenyl rings in the aroyldiarylcyclohexadiene moiety.

Attempts to separate the enantiomers (*R*)-**6** and (*S*)-**6** of the spiro[cyclohexadiene-dihydroacridines] by liquid chromatography were started using triacetylcellulose as the sorbent and methanol as the eluent. With the exception of **6f**, no separation could be achieved (cf. Table 1). Much better results were obtained with the sorbent *tris*-(3,5-dimethylphenylcarbamoyl)-cellulose on silica gel (Chiralcel OD™, eluent: *n*-heptane/2-propanol), allowing the separation of **6a–c** and **6f–j**.

Table 1. Chromatographic parameters for the separation of enantiomers of spiro[cyclohexadiene-dihydroacridines] **6** by liquid chromatography on different sorbents at 15-25°C; k'_1, k'_2: retention factors of enantiomers [9]; *Z*: Sign of rotation at 260 nm or 275 nm of the first eluted enantiomer; $\bar{k}'$: mean retention factor [9]

	Triacetylcellulose[a]			*Tris*-(3,5-dimethylphenylcarbamoyl)-cellulose on silica gel (Chiralcel OD™)[b]			(+)-Poly-(trityl methacrylate) on silica gel[b]		
	$k'_1(Z)$	k'_2	$\bar{k}'$	$k'_1(Z)$	k'_2	$\bar{k}'$	$k'_1(Z)$	k'_2	$\bar{k}'$
6a			0.9	0.6 (+)	0.7		1.2 (−)	2.6	
6b			0.8	0.5 (+)	0.6		1.1 (−)	2.7	
6c			1.1	1.0 (+)	1.1		1.9 (−)	3.6	
6d			0.9			0.6	1.1 (−)	3.7	
6e			1.0			0.6	1.1 (−)	4.3	
6f	1.0 (−)	1.4		0.6 (+)	1.0				1.4
6g			0.6	0.5 (+)	0.9				1.2
6h			1.0	0.6 (+)	0.9				1.2
6i			0.7	1.4 (−)	1.8		4.0 (+)	16.3	
6j			0.5	1.3 (+)	1.6		1.7 (+)	2.6	
6k			0.8			1.2	1.8 (+)	4.6	
6l			0.8			1.3	1.9 (+)	4.8	

[a] Eluent: methanol; [b] eluent: *n*-heptane/2-propanol (v : v = 9 : 1)

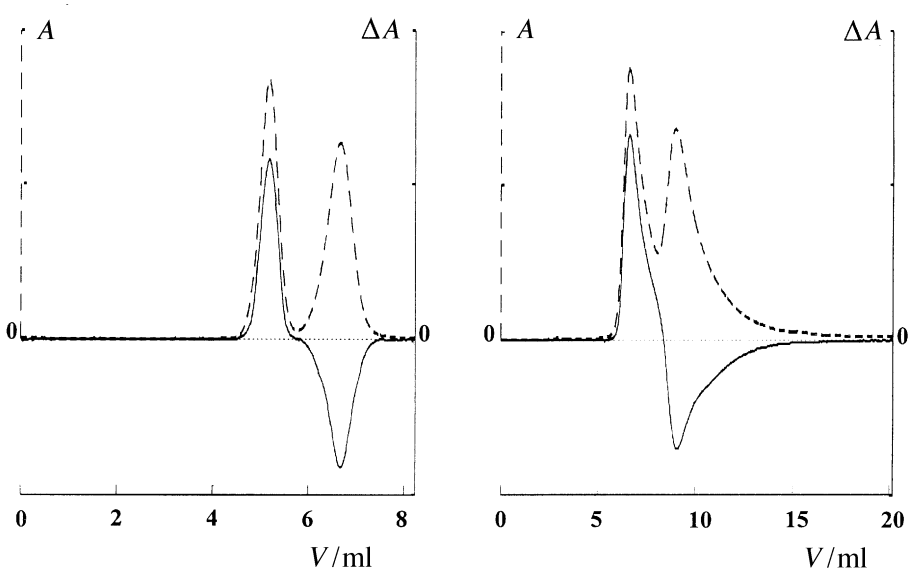


Fig. 1. Chromatograms of the spiro[cyclohexadiene-dihydroacridines] **6f** (left, 5 µg in *n*-heptane/2-propanol (v : v = 9 : 1) on *tris*-(3,5-dimethylphenylcarbamoyl)-cellulose/silica gel (Chiralcel OD^{TM})) and **6j** (right, 10 µg in *n*-heptane/2-propanol (v : v = 9 : 1) on (+)-poly-(trityl methacrylate)/silica gel; A and ΔA: absorbance and differential absorbance at 275 nm using the Jasco CD-1595 detector, V: volume of eluate ($V = 0$ upon injection)

The remaining spiro compounds **6d**,**e** and **6k**,**l** were successfully separated on (+)-poly-(trityl methacrylate) on silica gel (eluent: *n*-heptane/2-propanol). This system also worked well in the cases of **6a–c** and **6i**,**j** but was unable to separate **6f–h**. Furthermore, these investigations showed that obviously no connection exists between the substitution of the nitrogen atom in **6**, *i.e.* the presence of a secondary or a tertiary amine structure, and the result of the separation on different sorbents. Representative examples of the chromatograms of both types of compounds are shown in Fig. 1.

For the thermal racemizations, the spiro[cyclohexadiene-dihydroacridines] **6a**, **f**,**g** (R = Me) and **6i–k** (R = H) were chosen. The half-life times $t_{0.5}$ and the values of the free enthalpy of enantiomerization $\Delta G^{\neq}$ obtained are summarized in Table 2.

Table 2. Results of thermal racemization of spiro[cyclohexadiene-dihydroacridines] **6** in 1-propanol as monitored by polarimetry at 436 nm; $t_{0.5}$: half-life time, $\Delta G^{\neq}$: free enthalpy of activation for ring opening

	$T \pm 0.5/^{\circ}$C	$t_{0.5}$/min	$\Delta G^{\neq} \pm 0.2$/kJ · mol^{-1}
6a	69.6	453.8	114.5
6f	69.0	150.8	111.2
6g	69.6	626.8	115.4
6i	69.6	33.7	107.1
6j	69.0	58.5	108.5
6k	69.6	14.5	104.7

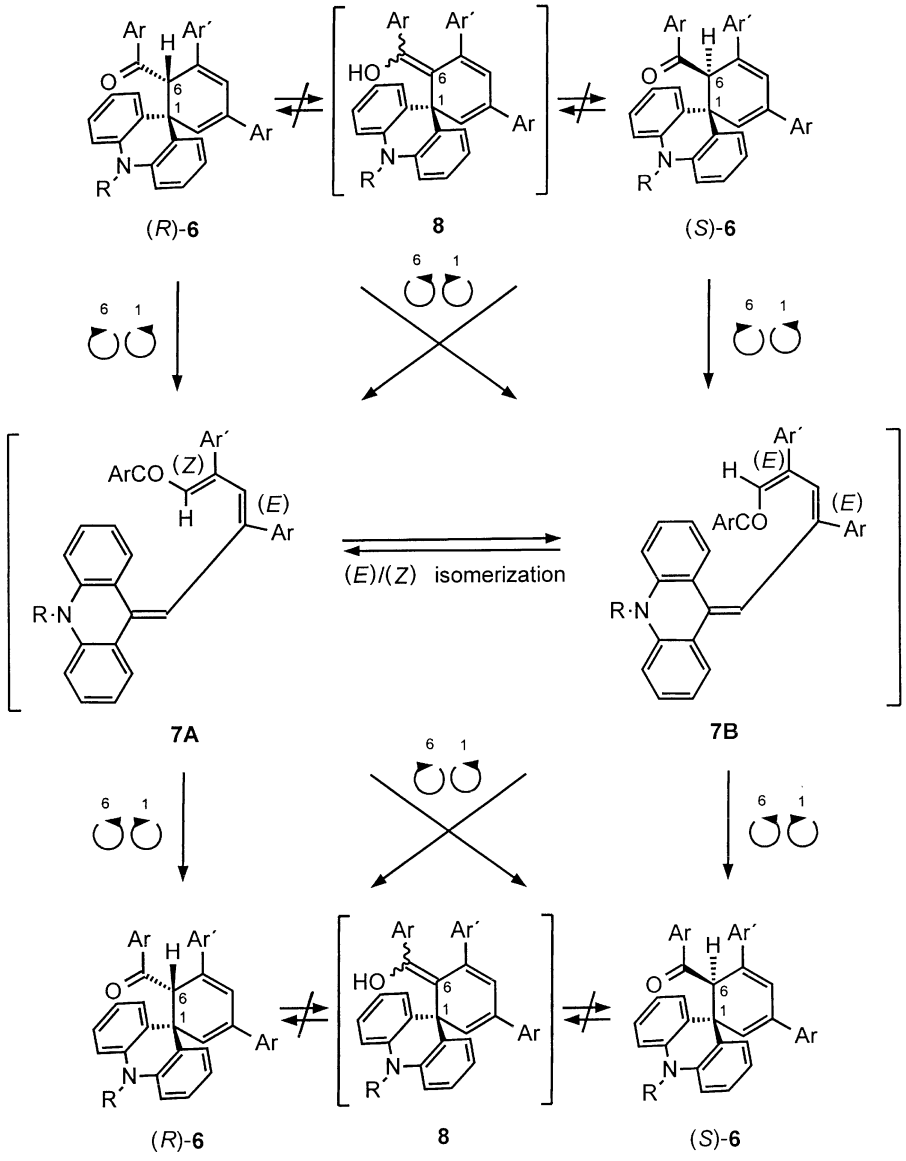
In the case of the N-methyl substituted derivatives **6a**,**f**,**g** the interconversion of the enantiomers occurs with a free enthalpy of activation $\Delta G^{\neq}$ comparable to that obtained for spiro[cyclohexadiene-indolines], in which the dihydroacridine system is replaced by an indoline moiety [7], as well as for structurally related spiro[indoline-chromenes] [8]. The exchange of the methyl substituent at the nitrogen atom by hydrogen in **6i–k** is accompanied by a decrease of the activation barrier. Obviously, the more basic tertiary amines **6a**,**f**,**g** can be better stabilized by hydrogen bonding with the OH-group of 1-propanol used as solvent than the secondary amines **6i–k**, thus leading to smaller $\Delta G^{\neq}$ values upon going from **6a**,**f**,**g** to **6i–k**. In both series of compounds, the activation parameters are not significantly influenced by the nature of the substituents at the phenyl rings.

At first glance one may assume that the interconversion of the enantiomers (*R*)-**6** and (*S*)-**6** occurs *via* enols of type **8**. The acidic enol hydrogen of **8** should be exchangeable by deuterium in the presence of deuterium donors. When the spiro[cyclohexadiene-dihydroacridines] **6a** and **6i** were refluxed in ethanol-OD and triethylamine or triethylamine/acetic acid-d_4, respectively, it could be shown by ^{1}H NMR spectroscopy (cf. Experimental) that no deuterium incorporation at C-6 had occurred, thus ruling out the enolization path.

An alternative mechanism for the thermal interconversion of the enantiomers (*R*)-**6**/(*S*)-**6**, which has already been discussed for the explanation of the thermal racemization of the structurally related spiro[cyclohexadiene-indolines] [7], consists of an electrocyclic ring opening to the merocyanines **7**, followed by an electrocyclic ring closure to the starting spiro compounds **6**. According to the *Woodward-Hoffmann* rules for electrocyclic processes [10], a disrotatory ring opening of (*R*)-**6** with a clockwise rotation of the orbitals at C-6 and an *anti*-clockwise rotation of those at C-1 (cf. Scheme 2) should give the merocyanine **7A**, the double bonds of which show the configurations (*E*) and (*Z*). The disrotatory ring opening in the opposite direction would give rise to the merocyanine **7B** where the double bonds are in (*E*)-configurations. Both merocyanines **7A** and **7B** can also be formed from the enantiomer (*S*)-**6** by disrotatory ring openings with the opposite directions of rotation at C-1 and C-6. The reactions (*R*)-**6** → **7A** and (*S*)-**6** → **7A** should have the same activation energy since during the cleavage of the C1-C6 single bond the same substituents approach each other or move away from each other. For the reactions (*R*)-**6** → **7B** and (*S*)-**6** → **7B**, one may again assume the same activation energy which, however, differs from that for the ring opening (forming **7A**), since the moving groups are not the same in both cases.

From the data obtained by our experiments it cannot be decided which of these ring opening reactions is favoured and hence which of the merocyanines, **7A** or **7B**, is formed a an intermediate. On the other hand, the charge delocalization in merocyanines usually leads to low barriers of (*E*)/(*Z*) isomerization [11], *i.e.* an interconversion of the merocyanines **7A**/**7B** cannot be excluded.

For the disrotatory ring closures of **7A** and **7B**, analogous considerations can be made (cf. Scheme 2). However, we assume that ring opening, not ring closure, is the rate determining step, corresponding to the experimental $\Delta G^{\neq}$ values in Table 2.



Experimental

The synthesis of the spiro[cyclohexadiene-dihydroacridines] **6a–l** has been described in a previous paper [4]. Ethanol-OD ($99.30 \pm 0.10\%$ D) and acetic acid-d_4 ($99.10 \pm 0.10\%$ D) were purchased from Deuchem, Leipzig, Germany. The ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer at 199.975 MHz in $CDCl_3$ at room temperature.

Deuterium exchange experiments

The spiro[cyclohexadiene-dihydroacridines] **6a** (258 mg, 0.5 mmol) and **6i** (251 mg, 0.5 mmol), respectively, were refluxed with 51 mg (0.5 mmol) of triethylamine, 5 cm^3 of ethanol-OD, and 5 cm^3 of toluene for 2 h. In a third and fourth experiment, 32 mg (0.5 mmol) of acetic acid-d_4 were added, the reaction mixtures were evaporated to dryness *in vacuo*, and the resulting residues were dissolved

in $CDCl_3$. ^1H NMR analyses showed that no deuterium exchange of the proton at C-6 [4] had occurred within error limits.

Chromatography

HPLC was performed on triacetylcellulose (Merck, 10 µm; column 250 × 8 mm; eluent methanol, flow rate 1 $cm^3 \cdot min^{-1}$, pressure 75 bar; room temperature), on *tris*-(3,5-dimethylphenylcarbamoyl)-cellulose/silica gel (Chiralcel OD™) (Daicel, 20 µm; column 250 × 4.6 mm; eluent *n*-heptane/2-propanol, 9 : 1 (*v*/*v*), flow rate 0.5 $cm^3 \cdot min^{-1}$, pressure 3 bar; room temperature), and on (+)-poly-(trityl methacrylate)/silica gel (Daicel, 5 µm; column 250 × 4 mm; eluent *n*-heptane/2-propanol, 9 : 1 (*v*/*v*), flow rate 1 $cm^3 \cdot min^{-1}$, pressure 120 bar; 15°C).

For photometric detection the UV spectrometers ERC 7210 and ERC 7215 (Erma Optical Works, Ltd.), and for polarimetric detection the polarimeter Perkin-Elmer 241 were used. Detailed descriptions of the injection and detector systems along with the chromatographic equipment have been given previously [8,12]. The chromatograms shown in Fig. 1 were obtained using the Jasco CD-1595 detector [13,14].

Thermal racemizations and data processing

Racemization of **6a**,**f**,**g** and **6i–k** was monitored in 1-propanol by an off-line procedure, *i.e.* the enantiomers were enriched at a semipreparative scale by repeated chromatography as described above and then dissolved in 1-propanol. The polarimetric cell which contained the solution of the enriched enantiomer was thermostated to the given temperature, and the decrease of the angle of rotation was monitored. The thermal stability was checked by chromatography after thermal racemization; in all cases the chromatograms obtained were identical with those of the starting compounds, thus indicating that no decomposition had occurred. The interconversion of the enantiomers was treated as a reversible first-order reaction as previously described [8]. A computer program [15] was used for the calculation of $\Delta G^{\neq}$ for the ring opening [8] (Table 2) from the polarimetric racemization data.

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