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Syntheses, Separation of Enantiomers and Barriers to Racemization of Some Sterically Hindered N-Aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinediones and Their Thio Analogues

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Summary. The novel N-aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinediones **1**, **4** and **8** were thiated with Lawesson reagent and P_4S_{10} to yield the monothio derivatives **2** and **5** and the dithio compounds **3**, **6** and **9**. Their enantiomers were separated by liquid chromatography on triacetyl- or tribenzoylcellulose. Rotation barriers for **1–4** and **8** were determined by thermal racemization and discussed in terms of steric effects.

Keywords. N-Aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinediones; N-Aryl-1,2,3,4-tetrahydro-3,3-dimethyl-quinoline-2-one-4-thiones; N-Aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinoline-dithiones; Enantioselective chromatography.

Synthese, Enantiomerentrennung und Barrieren zur Racemisierung einiger sterisch gehinderter N-Aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-chinolindione und ihrer Thio-Analogen

Zusammenfassung. Die neuen N-Aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-chinolindione **1**, **4** und **8** wurden mit Lawesson-Reagens und P_4S_{10} zu den Monothioderivate **2** und **5** und den Dithioverbindungen **3**, **6** und **9** thioniert. Ihre Enantiomeren wurden mittels Flüssigchromatographie an Triacetyl- oder Tribenzoylcellulose getrennt. Die Rotationsbarrieren für **1–4** und **8** wurden mittels thermischer Racemisierung bestimmt und aufgrund der sterischen Gegebenheiten diskutiert.

Introduction

In connection with our previous studies on atropisomeric N-aryl-2(1*H*)-quinolones and N-aryl-6(5*H*)-phenantridinones [1] we have prepared the novel N-aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinediones and their thio analogues **1–10**.

The ground state of these molecules is non-planar due to restricted rotation about the C–N bond, which gives rise to chirality. The principal aim of this study was to separate enantiomers (*M*) and (*P*) of **1**–**10** in order to study substituent effects upon the barriers to racemization. *Note*: the formula scheme refers to racemates (*M*, *P*), although (*M*) enantiomers are given exclusively.

Results

Synthetic Work

The novel N-aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinoline diones **1**, **4**, **7**, **8** and **10** (Table 1) were prepared by the methylation of the corresponding N-aryl-4-

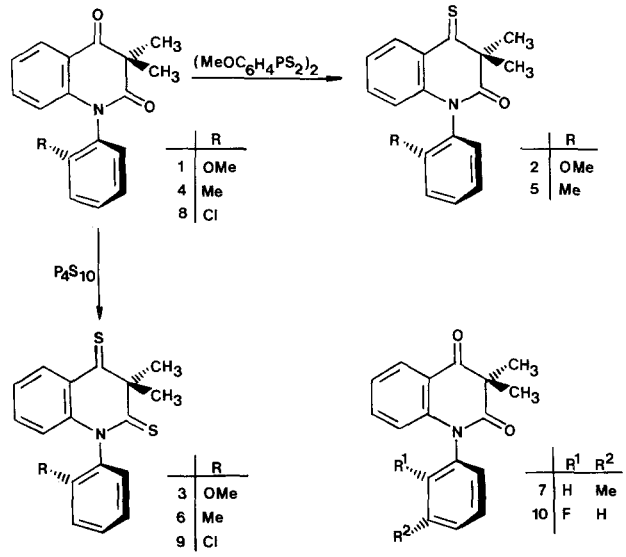


Table 1. Analytical and UV-spectral data

	Formula	M.p./°C	Found (calc.) % C	H	N	λ_{max} [nm][c] (log ε)
1	$C_{18}H_{17}NO_3$	183–184[a]	73.20 (73.22)	5.66 (5.81)	4.57 (4.57)	332 (3.55), 260 (3.82)
2	$C_{18}H_{17}NO_2S$	140–142[b]	69.36 (69.43)	5.73 (5.51)	4.48 (4.50)	395 (3.60), 315 (3.77), 255 (3.68)
3	$C_{18}H_{17}NOS_2$	177–178[b]	65.91 (66.02)	5.43 (5.23)	4.17 (4.28)	419 (3.63), 295 (4.12)
4	$C_{18}H_{17}NO_2$	155–157[a]	77.27 (77.38)	5.94 (6.14)	4.92 (5.01)	330 (3.93), 250sh (3.82)
5	$C_{18}H_{17}NOS$	111–112[b]	72.99 (73.19)	5.97 (5.80)	4.70 (4.74)	390sh (2.85), 325 (3.49) 250sh (3.93)
6	$C_{18}H_{17}NS_2$	172–174[b]	69.20 (69.41)	5.31 (5.50)	4.47 (4.50)	415 (3.58), 294 (4.14)
7	$C_{18}H_{17}NO_2$	129–131[a]	77.15 (77.38)	6.24 (6.14)	5.25 (5.01)	328 (3.40), 265sh (3.62)
8	$C_{17}H_{14}ClNO_2$	123–125[a]	68.37 (68.12)	4.51 (4.71)	4.82 (4.67)	330 (3.40), 260sh (3.76)
9	$C_{17}H_{14}ClNS_2$	160–162[b]	61.37 (61.52)	4.08 (4.25)	4.37 (4.22)	412 (3.71), 292 (4.35)
10	$C_{17}H_{14}FNO_2$	164–166[a]	70.60 (72.07)	5.14 (4.98)	5.04 (4.94)	325 (3.60), 255sh (3.87)

[a] Obtained by repeated recrystallization from EtOH

[b] Isolated by column chromatography on silica gel (0.063–0.2 mm) with light petroleum 40–70 °C)

[c] In absolute MeOH at 25 °C

hydroxy-3-methyl-2(1*H*) quinolones [1] with methyl iodide and moist silver oxide in dimethylformamide by a general method described by Kuhn et al. [2]. The methylation occurred at the position C-3 of the heterocyclic ring which is in accord with an earlier observation that in some 4-hydroxy-2(1*H*)-quinolones C-alkylation competes with O-alkylation [3]. The monothio derivatives **2** and **5** were prepared by thiation of the corresponding quinoline-2,4-diones **1** and **4** with Lawesson reagent [4] in refluxing toluene. The dithio derivatives **3**, **6**, and **9** were obtained by thiation of the corresponding quinoline-2,4-diones **1**, **4** and **8** with P_4S_{10} in refluxing toluene.

^1H *and* ^{13}C *NMR*

In order to prove the structures of the novel compounds **1–10**, their ^1H and ^{13}C NMR spectra were examined in detail (Tables 2 and 3). The ^1H NMR spectra of **1–10** showed close similarity of all comparable signals through the series. The

Table 2. ^1H NMR chemical shifts δ_H/ppm and coupling constants J (Hz) for **1–10** in $CDCl_3$ at 22 °C[a]

	R^1	R^2	X	Y	3-CH_3	5-H	8-H	Benzo
1	OCH_3 3.8(s)	H	O	O	1.6(s)	8.1(dd) $^3J = 8.2$ $^4J = 2.0$	6.4(dd) $^3J = 8.2$ $^4J = 2.0$	7.0–7.6(m)
2	OCH_3 3.8(s)	H	O	S	1.7(s) 1.8(s)	8.3(dd) $^3J = 8.2$ $^4J = 1.4$	6.4(dd) $^3J = 8.3$ $^4J = 0.7$	7.0–7.5(m)
3	OCH_3 3.8(s)	H	S	S	1.83(s) 1.95(s)	8.2(dd) $^3J = 7.9$ $^4J = 1.5$	6.4(dd) $^3J = 8.2$ $^4J = 1.2$	7.0–7.6(m)
4	CH_3 2.1(s)	H	O	O	1.6(s)	8.1(dd) $^3J = 7.4$ $^4J = 1.8$	6.3(dd) $^3J = 8.5$ $^4J = 1.1$	7.0–7.5(m)
5	CH_3 2.1(s)	H	O	S	1.7(s) 1.8(s)	8.3(dd) $^3J = 7.9$ $^4J = 1.8$	6.3(d) $^3J = 8.2$	7.1–7.4(m)
6	CH_3 2.1(s)	H	S	S	1.8(s) 2.0(s)	8.2(d) $^3J = 7.7$	6.3(d) $^3J = 8.2$	7.1–7.4(m)
7	H 6.2(s)	CH_3 2.2(s)	O	O	1.6(s)	7.9(d) $^3J = 8.1$	6.9(d) $^3J = 8.1$	7.2–7.8(m)
8	Cl	H	O	O	1.60(s) 1.62(s)	8.1(dd) $^3J = 7.3$ $^4J = 1.8$	6.3(dd) $^3J = 7.6$ $^4J = 0.9$	7.2–7.6(m)
9	Cl	H	S	S	1.84(s) 1.97(s)	8.1(dd) $^3J = 8.1$ $^4J = 1.5$	6.3(d) $^3J = 8.3$	7.1–7.6(m)
10	F	H	O	O	1.6(s)	8.1(dd) $^3J = 7.9$ $^4J = 1.8$	6.5(d) $^3J = 8.2$	7.1–7.6(m)

[a] Digital resolution 0.29 Hz, 8 K addresses and 1200 Hz sweep width

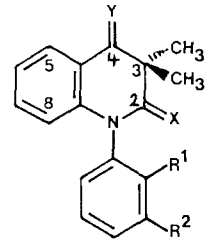


Table 3. ^{13}C NMR chemical shifts δ/ppm for **1–10** in $CDCl_3$ at 22 °C[a]

	R^1	R^2	X	Y	3-CH_3	C-2	C-3	C-4	C-benzo
1	OCH_3 55.5	H	O	O	22.0 24.7	173.6	53.5	197.4	112.2, 115.7, 119.1(q), 121.2, 122.6, 125.4(q), 127.5, 130.0, 130.2, 135.2, 143.5(q), 155.2(q).
2	OCH_3 55.9	H	O	S	27.2 30.2	173.8	61.5	239.1	112.7, 116.4, 121.8, 123.3, 126.2(q), 129.1(q), 130.4, 130.6, 130.7, 135.0, 139.5(q), 155.9(q).
3	OCH_3 56.0	H	S	S	31.7 31.9	209.1	66.8	239.7	113.0, 117.2, 121.9, 124.4, 129.4, 130.0, 130.4, 130.5, 130.8(q), 131.3(q), 137.6(q), 159.4(q).
4	CH_3 17.9	H	O	O	22.6 24.9	173.7	53.8	197.6	116.1, 119.5(q), 123.2, 127.9, 128.2, 128.9, 129.2, 131.7, 135.7, 136.3(q), 136.6(q), 143.4(q).
5	CH_3 17.3	H	O	S	27.5 29.9	173.1	61.4	238.3	116.0, 123.3, 127.9, 128.7, 128.9(q), 129.1, 130.6. 131.6, 134.9, 136.4(q), 138.6(q)
6	CH_3 17.2	H	S	S	31.8 33.4	207.7	66.5	238.3	117.2, 124.6, 127.9, 128.1, 129.0, 130.0, 130.8(q), 131.6, 134.5, 135.7(q), 136.9(q), 141.4(q)
7	H	CH_3 23.8	O	O	22.1 23.8	174.7	53.5	197.1	116.9, 117.3(q), 124.3, 128.1, 128.8, 129.0, 130.2. 137.7(q), 144.1(q), 146.8(q)
8	Cl	H	O	O	21.5 25.7	173.6	53.9	197.3	115.7, 119.5(q), 123.5, 128.2, 128.6, 130.5, 130.9, 131.0, 134.8(q), 133.6(q), 135.6, 143.8(q).
9	Cl	H	S	S	31.0 34.0	208.1	66.9	238.5	116.0, 124.8, 128.8, 130.1, 130.2, 130.2, 130.8(q), 131.1, 132.9(q), 134.6, 136.7(q), 139.8(q).
10	F	H	O	O	22.3 25.1	174.3	54.1	197.6	116.0, 117.5 (d, $J_{C-F} = 78.3$ Hz) 119.8(q), 123.7, 125.7 (d, $J_{C-F} = 16$ Hz), 128.5, 131.1, 131.3 (d, $J_{C-F} = 31$ Hz) 135.8, 143.4(q), 157.3(q), 160.7(q)

[a] The assignments of C-2, C-3, C-4, 3-CH_3 and the quarternary C-atoms (q) in the spectra of **1**, **2**, **4** and **8–10**, and **3–7** were confirmed by APT and DEPT spectra, respectively; J_{C-F} means carbon fluorine coupling constant and d doublet

high-field position of the diagnostic quinoline signal [5] 8-H in all spectra ($\delta = 6.3$–6.9) may be explained by the anisotropic effect of the adjacent N-aryl group. The 5-H signal appears at lower field ($\delta = 7.9$–8.3) than 8-H owing to the proximity of 5-H to the carbonyl oxygen and thiocarbonyl sulfur in **1**, **4**, **7**, **8** and **10**, and **2**, **3**, **5**, **6** and **9**, respectively. The two 3-CH_3 groups in **2**, **3**, **5**, **6**, **8**, and **9** display unequal chemical shifts, i.e., they are *diastereotopic*. However, both 3-CH_3 signals in **1**, **4**, **7**, and **10** appear at the same field by coincidence, i.e., they are accidentally *isochronous*. The signals of both 3-CH_3 groups in the monothio derivatives **2** and **5** appear at lower field than those of the corresponding diketo derivatives **1** and **4**. That is due to the deshielding effect of one adjacent thiocarbonyl group at the position C-4 of the heterocyclic ring in **2** and **4**. Consistently, the 3-CH_3 signals in the dithio compounds **3**, **6**, and **9** are shifted to lower fields than those of the corresponding monothio- and diketo compounds. That is due to the deshielding effect of *two* adjacent thiocarbonyl groups to 3-CH_3 in **3**, **6**, and **9**. These assignments are in good agreement with structurally related N-aryl-2(1*H*)-quinolones [1]. The comparison of the ^{13}C NMR spectral data in Table 2 shows that in all spectra the two 3-CH_3 groups are diastereotopic. The C-4 signal appears in the spectra of the monothio compounds **2** and **5** at lower field ($\delta = 239.1$ and 238.3, respectively) than in the diketo derivatives **1** and **4** ($\delta = 197.4$ and 197.6). This is due to a deshielding effect of the thiocarbonyl sulfur. As a consequence of substitution of both carbonyls by thiocarbonyl groups in the dithio compounds **3**, **6**, and **9**, the C-2, C-4 and 3-CH_3 signals are shifted to lower fields than those of the corresponding diketo derivatives **1**, **4**, and **8**. The assignments in the spectra of **1**, **2**, **4**, and **8**–**10** were deduced from their attached-proton-test (APT) spectra. Distortionless enhancement by polarization transfer (DEPT) [6] experiments were also performed for the assignments of **3** and **7**. The comparison with the ^{13}C NMR spectra of structurally related compounds such as 1-(2′-methylphenyl)-4,6-dimethylpyrimidine-2-one and the corresponding 2-thione derivative [7], as well as 3-benzyl-3-ethyl-1,2,3,4-tetrahydro-quinoline-2,4-dione [8] is consistent with the assignments in Table 2.

UV Spectra

Comparison of the UV spectral data in Table 1 shows that the monothio derivatives **2** and **5** exhibit an absorption band at 395 and 390 nm, respectively, which is at longer wavelength than that of the corresponding diketo derivatives **1** and **4**. This band may be assigned to the n-π^* transition of the thiocarbonyl group at the position C-4 of the heterocyclic ring. The quinoline-2,4-dithiones **3**, **6**, and **9** exhibit an absorption band in the region 412–419 nm whereas the corresponding diketo derivatives **1**, **4**, and **7** have an absorption band at shorter wavelength (328–332 nm). Analogously, that band may be assigned to the n-π^* transition of the thiocarbonyl groups of the heterocyclic ring. Such a transition is similar to the n-π^* transition of the carbonyl group but at longer wavelengths because the ionization potential of the sulfur lone pair is lower than that of the oxygen lone pair. Similarly, the second absorption band is found in the UV spectra of **3**, **6**, and **9** in the region 292–295 nm, i.e., at longer wavelengths than in the corresponding diketo derivatives **1**, **4** and **7**. This more intense absorption band may be ascribed to a π-π^* transition which

is in accord with earlier results on the electronic transition of the thiocarbonyl group [9].

Separation and Racemization of Enantiomers

Liquid chromatography (l.c.) on triacetylcellulose (TAC) or tribenzoylcellulose (TBC) monitored by u.v. and polarimetric detection was used for separation of enantiomers of the compounds. Capacity factors [1, 10] k' which correspond to stabilities of diastereomeric sorbates, and relative retentions of enantiomers [1, 10] α', are summarized in Table 4. A complete or an almost complete separation of

Table 4. Chromatographic parameters for the separation of enantiomers by liquid chromatography at 22–25 °C. k' capacity factors of enantiomers [1, 10]. Z: Sign of rotation at 365 or 435 nm of first eluted enantiomer. α' Relative retention of enantiomers. k' Mean capacity factors [1, 10]

	k'_1(Z)	k'_2	α'	k'
(±)-**1**	1.4(−)[a]	3.8[a]	2.7[a]	
(±)-**2**	0.5(−)[c]	1.2[c]	2.4[c]	
(±)-**3**	1.1(−)[a]	1.5[a]	1.4[a]	
(±)-**4**	3.0(−)[a]	4.2[a]	1.4[a]	
(±)-**5**	2.4(−)[a]	4.9[a]	2.0[a]	
	0.7(−)[c]	2.5[c]	3.6[c]	
(±)-**6**	1.0(−)[a]	1.6[a]	1.6[a]	
	2.8(−)[b]	3.7[b]	1.3[b]	
(±)-**7**	–	–	–	5.9[a]
(±)-**8**	1.0(−)[d]	2.4[d]	2.4[d]	
	6.7(−)[e]	8.6[e]	1.3[e]	
(+)-**9**	1.6(−)[a]	2.7[a]	1.6[a]	
(+)-**10**	–	–	–	3.6[a]
	–	–	–	4.5[f]

[a] Low-pressure liquid chromatography (LPLC) on triacetylcellulose (TAC) as the sorbent and EtOH:H_2O (96:4) as the eluent. Obtained on different columns of the same type. According to our experience, the k' values are not exactly comparable in such cases, whereas the α' values can be compared

[b] LPLC on tribenzoylcellulose (TBC) as the sorbent and MeOH as the eluent

[c] LPLC on TAC as the sorbent and MeOH as the eluent

[d] High-pressure liquid chromatography (HPLC) on TAC as the sorbent and MeOH as the eluent

[e] HPLC on TAC as the sorbent and EtOH:H_2O (96:4) as the eluent

[f] HPLC on TBC as the sorbent and MeOH as the eluent

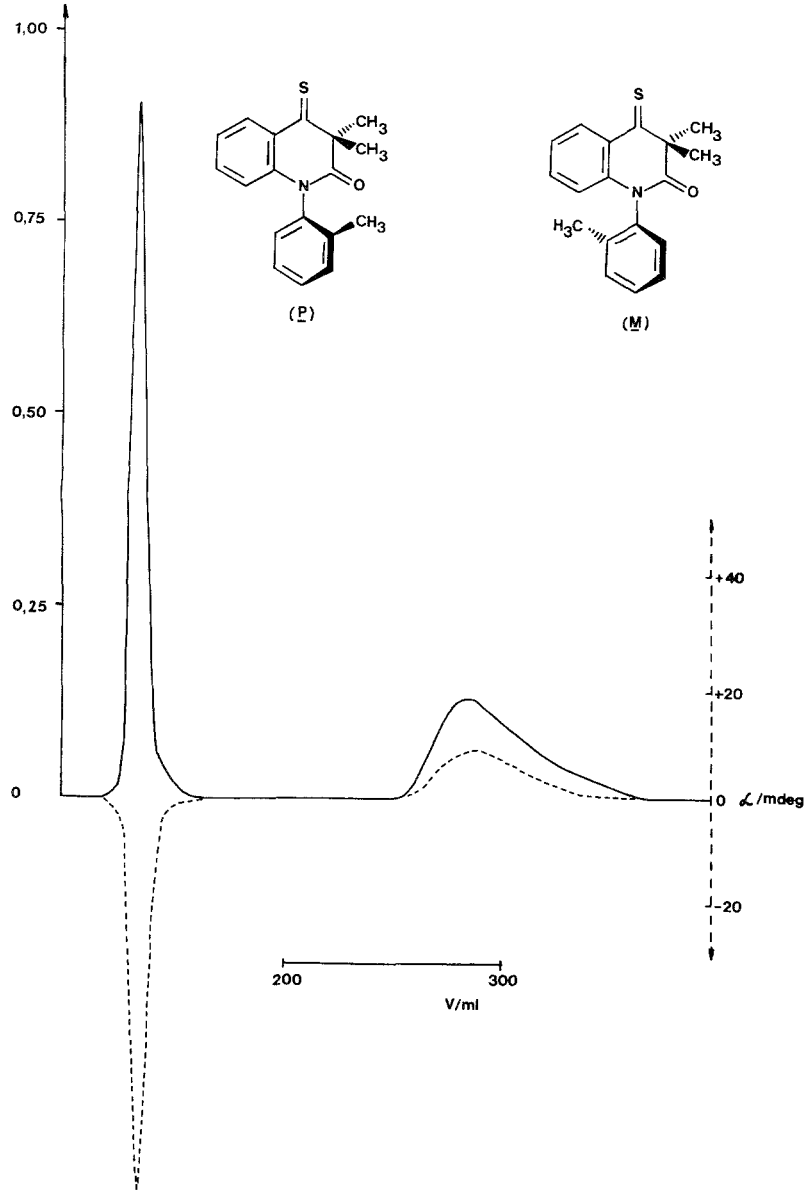


Fig. 1. Chromatogram of (*MP*)-**5** in MeOH on triacetylcellulose (particle size 0.02–0.03 mm). (– – – –) Δp = bar Rotational angle (α') at 546 nm; (———) Absorbance (A) at 254 nm; V volume of eluate; k' capacity factor

enantiomers was achieved for most of the compounds studied, that is for **1**–**6**, **8** and **9** (α' coefficients vary from 1.3–4). This can be illustrated by the analytical chromatogram of (*MP*)-**5** (Fig. 1) showing no overlap of the enantiomer peaks. An exception of such chromatographic behaviour was found in (*MP*)-**10** possessing an *N*-(*ortho*-fluorophenyl) group, which showed only marginal resolution of enantiomers by l.c. on TAC as well as on TBC. The compound **7** showed as expected no separation of enantiomers by l.c. on TAC. The barrier to rotation in **7** containing the *N*-(*meta*-methylphenyl) group is obviously not sufficiently high to give rise to

Table 5. Barriers to partial rotation about the C–N bond

	Solvent	T (°C)	$10^5 k^a$ (s^{-1})	λ^b (nm)	$\Delta G^{\neq}$ (kJ mol^{-1})
(*MP*)-**1**	ethanol-H_2O (96:4)	27	10.0	365	97.4 ± 0.2^c
(*MP*)-**2**	MeOH	30	9.8	546	97.6 ± 0.2^c
(*MP*)-**3**	diglyme	59	11.8	546	106.7 ± 0.2^d
(*MP*)-**4**	diglyme	74	60	436	106.9 ± 0.7^d
		64	20	436	107.0 ± 0.4^d
(*MP*)-**8**	diglyme	59	14.4	436	106.2 ± 0.2^d

[a] Rate constant

[b] Wavelength at which thermal recemization was monitored by polarimetry

[c] Obtained by an on-line procedure [11–13] using the solution of an enriched enantiomer in the polarimetric cell

[d] Obtained by thermal racemization of semipreparatively separated enantiomers

stable enantiomers which can then be separated by l.c. on an optically active stationary phase. Furthermore, one can observe that the first eluted enantiomer of all separated compounds in the series **1**–**10** is the levorotatory one. The Gibbs energy of activation, $\Delta G^{\neq}$, for restricted rotation about the C–N bond in **1** and **2** was obtained by an on-line procedure [11–13] using the solution of an enantiomerically enriched sample in the polarimetric cell (Table 5). The barriers to partial rotation [15] about the C–N bond in **3**, **4** and **8** (Table 5) were determined by thermal racemization of preparatively enriched enantiomers. However, we were not able to determine the racemization rate for the quinoline-2,4-dithione derivative **9** which showed decomposition during racemization under prolonged heating at 75 °C in diglyme. This was indicated by coloration of the solution and deviation from the linearity of the kinetic plot.

Discussion

Both analytical and spectroscopic data were consistent with the proposed structures **1**–**10**. The structures of compounds **1**, **4**, and **8** were unequivocally confirmed by their X-ray crystallographic analysis [14]. In our previous study on racemization barriers of atropisomeric N-aryl-2(1*H*)-quinolones and N-aryl-6(5*H*)-phenantridinones [1] we have proposed that an internal rotation about the C(sp2)–N(sp2) bond is the mechanism for the interconversion of enantiomers. We have estimated from molecular mechanics calculations that the energetically more favorable transition state for this rotation is the one in which the bulky ortho-substituents pass the carbonyl group rather than the benzo ring [15]. Such a mechanism may also account for the observed racemization processes in quinoline-2,4-dione and -thione derivatives **1**–**4** and **8**. Furthermore, we have found that the $\Delta G^{\neq}$ value for restricted rotation in 3-methoxy-2-methyl N-(2′-methylphenyl)-4-pyridone [11] is higher by 3.9 kJ mol^{-1} in EtOH-H_2O (96:4), due to the hydrogen bonding, than in diglyme.

If that difference is applied to the barrier of **1** measured in EtOH-H_2O (96:4), a $\Delta G^{\neq}$ value of approximately 94 kJ mol^{-1} may be estimated. That barrier may be compared qualitatively with the corresponding one of **3** in spite of somewhat different temperatures of racemization; even a moderately negative $\Delta S^{\neq}$ would not cause an essential change. Comparison shows that the barrier to racemization in **3** is higher by 13 kJ mol^{-1} compared to the one of the corresponding dione derivative **1**. That difference may be attributed to a more severe steric interaction in the transition state for the enantiomeric inversion in quinoline-2,4-dithione **3** than in **1**. This is consistent with a difference in the effective sizes of sulfur and oxygen as shown by the determination of the barriers to rotation of the N-isopropyl-4-isopropyl-5-methylthiazoline-2-thione and the corresponding thiazoline-2-one derivative [16]. The barrier to racemization in the thioketo compound **2** is almost the same as the one in the corresponding diketo derivative **1**. That means that substitution of the carbonyl group by the thiocarbonyl one at position C-4 of the heterocyclic ring has no influence on the racemization barrier. The $\Delta G^{\neq}$ value for restricted rotation about the C–N bond is slightly higher, i.e. 0.8 kJ mol^{-1} for the *ortho*-methyl derivative **4** than for *ortho*-chloro derivative 8 at otherwise practically the same temperatures. This slight difference may be ascribed to a greater steric effect of the methyl group than a chlorine atom in restricting internal rotation. This is in accord with the relative size of these groups as determined by X-ray crystallographic measurements of their van der Waals radii [17].

Experimental Part

Melting points were determined on a Kofler micro hot-stage (Reichert, Wien) and are not corrected. The UV spectra were recorded on a Beckman 24 and IR spectra on a Perkin–Elmer 297 Infracord spectrometer using KBr discs. The ^{1}H NMR spectra of **1**, **3–8** and **10** were recorded on Jeol FX-90 Q (PFT mode, 8 K data points, 90 MHz). The ^{1}H NMR spectra of **2** and **9** were taken on Bruker WH 250 (PFT mode, 32 K data points, MHz) and Varian XL GEM 300 (PFT mode, 300 MHz) spectrometers, respectively. The ^{13}C NMR spectra of **1**, **2**, **4**, and **8–10** were recorded on a Varian XL GEM 300 MHz spectrometer operating at 75 MHz for ^{13}C resonance. The techniques used were: broad band proton decoupling and *Attached Proton Test*. The ^{13}C NMR spectra of **3** and **7** were recorded on a Bruker WH 250 spectrometer operating at 61.5 MHz for ^{13}C resonance. In the latter case techniques used were: broad band proton decoupling and *Distortionless Enhancement by Polarization Transfer* [6]. The broad band proton decoupled ^{13}C NMR spectra of **5** and **6** were taken on a JEOL FX-90 Q spectrometer operating 22.5 MHz for ^{13}C resonance. The high resolution electron impact mass spectra (eims) of **3** and **6** were recorded on the EXTREL FT MS 2001 DD instrument, the ones of **10** on a Varian MAT 95 double focussing mass spectrometer with ionizing energy 70 eV. Elemental analyses were performed by the central analytical service, Institut "Rudjer Bošković", Zagreb. Analytical data are presented in Table 1.

Chromatography

Low-pressure liquid chromatography (column 300 × 25 mm) at flow rate 3.5–6.2 cm^3 min^{-1}, $\Delta p = 2.0$–3.6 bar, on triacetylcellulose or tribenzoylcellulose as stationary phases and methanol or ethanol:water 96:4 (*v/v*) as eluents were used for the separation of enantiomers (±)-**1**-(±)-**7**, (±)-**9** and (±)-**10**. High-pressure liquid chromatography (column 250 × 8 mm) at flow rate 1.5 cm^3 min^{-1}, $\Delta p = 50$–174 bar on triacetylcellulose or tribenzoylcellulose as stationary phases were used for the separation of enantiomers of (±)-**8** and (±)-**10**. Injected quantities of racemates were 2–6 mg in 1 cm^3

of the eluent. Sample injection and detector systems along with other details of the chromatographic equipment have been described previously [18].

Thermal Racemization of Enriched Enantiomers

Kinetics of racemization of **1** was performed in ethanol/H_2O (96:4) by an online procedure [11–13], i.e., a run of liquid chromatography was stopped when the polarimetric detection was high. The polarimetric cell which now contained the solution of an enriched enantiomer, was thermostated to a suitable temperature and the decrease of the angle of rotation was monitored. Racemization of **3**, **4**, and **8** were performed off line, i.e., preparatively separated samples of enantiomers were dissolved in diglyme (spectroscopic grade) and first-order kinetics were followed by monitoring the decrease of the rotation angle at the given temperature for the duration of 1.5–3 half lives. In all those cases good first-order plots were obtained.

N-(2'-Methoxyphenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinedione (**1**)

6.0 g (0.021 mol) of 4-hydroxy-3-methyl-N-(2'-methoxyphenyl)-2(1*H*)-quinolone which was prepared as described previously [1], were dissolved in approximately 25 ml of dimethylformamide and 3.9 g (0.017 mol) of moist silver oxide [19] were added portionwise while the solution was stirred vigorously. The flask was stopped and mechanically shaken for 48 h. The mixture was filtered, and the mother liquor diluted with 500 ml of distilled water. 3.0 g (0.045 mol) of potassium cyanide were then added, and the solution was extracted several times with chloroform. The chloroform extracts were dried with anhydrous magnesium sulfate and the solvent was evaporated. After trituration of the residual oil with ethanol the solidified product was obtained. Recrystallization from ethanol gave pure white crystals of **1**. IR: $\nu_{C=O}$(ketone) 1710, $\nu_{C=O}$(lactame) 1670 cm^{-1}. The other novel 2,4-quinolinediones **4**, **7**, **8**, and **10** were prepared by analogoues procedures.

N-(2-Methylphenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinedione (**4**)

IR: $\nu_{C=O}$(ketone) 1708, $\nu_{C=O}$(lactame) 1670 cm^{-1}. Yield 30%.

N-(3'-Methylphenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinedione (**7**)

Purification for analytical purposes was effected by column chromatography on silica gel with chloroform-light petroleum (30–50 °C) (1:1) as the solvent and repeated recrystallization of the separated crystalline product from EtOH. IR: $\nu_{C=O}$(ketone) 1710, $\nu_{C=O}$(lactame) 1672 cm^{-1}. Yield 20%.

N-(2'-Chlorophenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinedione (**8**)

IR: $\nu_{C=O}$(ketone) 1700, $\nu_{C=O}$(lactame) 1675 cm^{-1}. Yield 46%.

N-(2'-Fluorophenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinedione (**10**)

IR: $\nu_{C=O}$(ketone) 1710, $\nu_{C=O}$(lactame) 1680 cm^{-1}. MS: found M^+, 283,10035; calc. for $C_{17}H_{14}FNO_2$ 283,10086. Yield 36%.

N-(2'-Methoxyphenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-quinoline-2-one-4-thione (**2**)

0.5 g (0.0017 mol) of **1** were dissolved in 30 ml of absolute toluene and 1.6 g (0.004 mol) of the Lawesson reagent were added portionwise to this solution. The reaction mixture was heated under reflux for 2 h. Analysis of the reaction product by thin-layer chromatography on silica using chloroform-ethyl acetate

(5:1) as the solvent showed disappearance of the initial quinoline-2,4-dione **1**. The reaction mixture was then cooled to room temperature, the excess of the Lawsesson reagent was filtered off and the solvent removed from the mother liquor by evaporation. Purification of the resulting oily residue by column chromatography on silica gel with light petroleum (40–70 °C)-ethyl acetate (10:1) as the solvent gave purple crystals of 2. IR: $\nu_{C=O}$(lactame) 1680 cm^{-1}. Yield 43%.

N-(2'-Methylphenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-quinoline-2-one-4-thione (**5**)

Prepared by the procedure analogous to that for **2**. IR: $\nu_{C=O}$ 1670 cm^{-1}. Purple crystals were obtained. Yield 25%.

N-(2'-Methoxyphenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinoline-dithione (**3**)

0.9 g (0.0028 mol) of **1** were dissolved in 30 ml of absolute toluene and 0.7 g (0.0030 mol) of P_4S_{10} were added portionwise while the solution was heated under reflux. The reaction mixture was then additionally heated under reflux for 24 h. The solvent was removed by evaporation and the residue extracted several times with chloroform. The chloroform extracts were washed with water and dried over anhydrous magnesium sulfate. After removing the solvent by evaporation an oily residue was obtained. Purification by column chromatography on silica gel with light petroleum (40–70 °C)-chloroform (10:1) as the solvent gave 0.25 g of green crystals of 3. Yield 24%. MS: found 327.069282; calc. for $C_{18}H_{17}NOS_2$ 327.074609. (Table 1). The other dithio derivatives **6** and **9** were prepared by analogous procedures.

N(2'-Methylphenyl)-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinedithione (**6**)

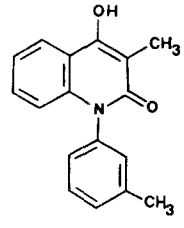
Green crystals were obtained. MS: found 311.080976; calc. for $C_{18}H_{17}NS_2$ 311.079694. Yield 4%.

N-(2'-Chlorophenyl)-3,3-dimethyl-1,2,3,4-tetrahydro-2,4-quinoline-dithione (**9**)

Green crystals were obtained. Yield 27%.

N-(3'-Methylphenyl)-4-hydroxy-3-methyl-2(1H)quinolone (**11**)

This was prepared by an analogous procedure to that described for the N-(2'-fluorophenyl)-4-hydroxy-3-methyl-2(1*H*)-quinolone [1]. After recrystallization from ethanol the pure crystals of **11**, m.p. 268–270 °C were obtained. Elemental analysis: found C 76.94, H 5.65, N 5.30; calc. for $C_{17}H_{15}NO_2$ C 76.96, H 5.70, N 5.28%. Yield 20%.



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