Tetrahedron Vol. 41, No. 1, pp. 229 to 233, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

ENANTIOMERS OF STERICALLY HINDERED N-ARYL-4-PYRIDONES

CHROMATOGRAPHIC ENRICHMENT AND THERMAL INTERCONVERSION†‡

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(*Received in UK* 21 *May* 1984)

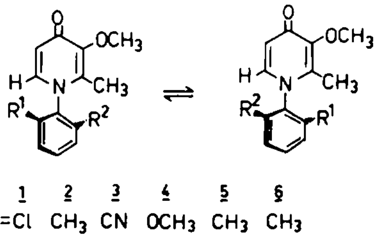
Abstract—N-Aryl-4-pyridones **1–6** were synthesized by condensation of the corresponding 4-pyrone with anilines. The enrichment of the enantiomers was achieved by liquid chromatography on triacetylcellulose, enantiomeric purities of (+)-**1** and (+)-**2** being measured by ^{1}H-NMR in the presence of an optically active auxiliary. Barriers to partial rotation about the C—N bond in **1–4** were determined and compared with corresponding biphenyls.

As a result of restricted rotation about the C—N bond between the aryl and pyridone rings, the ground state of substituted N-aryl-4-pyridones (Scheme 1) is not planar. Consequently, the condition for chirality is fulfilled. Provided that the barrier to rotation is sufficiently high, separation of rotational enantiomers should be possible. There were no reported data about such optically active heterocycles, except some N-aryl-4,6-dimethyl-2(1H)-pyrimidinones and -thiones (see below), the rotational isomers of which were separated by classical resolution *via* diastereomeric salts.[3] Since liquid chromatography (LC) on triacetylcellulose[4] had been successfully applied to other twisted molecules,[1,2,5,6] we used this method for the separation of enantiomers of **1–5**, needed for the measurement of barriers to partial rotation about their C—N bond.

Synthesis and enrichment of enantiomers

Pyridones **1–6** (Scheme 1) were synthesized by thermal condensation of 3-methoxy-2-methyl-4-pyrone with a 10% excess of the corresponding aniline.[7] Semi-preparative enrichments by LC of the enantiomers of (±)-**1** and (±)-**2** with enantiomeric purities (see below) of 56% and 24%, respectively, were obtained. The weak separations, low angles of rotation and high absorbances of all our pyridones can be illustrated by the chromatogram of (±)-**1** (Fig. 1). The experiments with (±)-**4** and (±)-**5** yielded only marginal semi-preparative enrichments. Attempts to obtain preparatively enriched enantiomers of (±)-**3** were not successful. A possible explanation for the deviation of (±)-**3** and (±)-**4** from the behaviour of (±)-**1** and (±)-**2** could be their lower barriers to rotation (see below).

The chemical purity of the isolated enantiomers was confirmed by ^{1}H-NMR. ^{1}H-NMR in the presence of the optically active auxiliary (+)-1-(9-anthryl)-2,2,2-trifluoroethanol served for determination[8] of enantiomeric purities P of (+)-**1** (Fig. 2) and (+)-**2** by computer simulation[9] of the unequal intensities of the



	1	2	3	4	5	6
R^1=	Cl	CH_3	CN	OCH_3	CH_3	CH_3
R^2=	H	H	H	H	Cl	CH_3

Scheme 1.

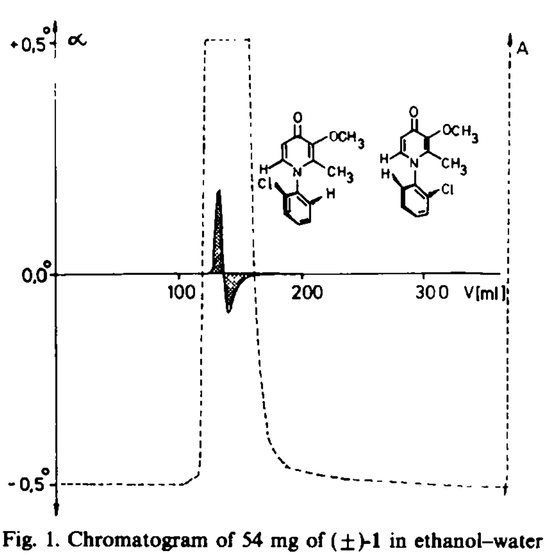


Fig. 1. Chromatogram of 54 mg of (±)-**1** in ethanol–water (96:4) after passing a column of triacetylcellulose (particle size 0.032 to 0.056 mm). α: Rotation angle (——) at 365 nm; A: absorbance (-----) at 254 nm; V: volume of eluate.

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† Paper presented at the 29th International Congress of Pure and Applied Chemistry, Cologne, 1983.

‡ Liquid Chromatography on Triacetylcellulose, Part, 9. Part 8;[1] Part 7.[2]

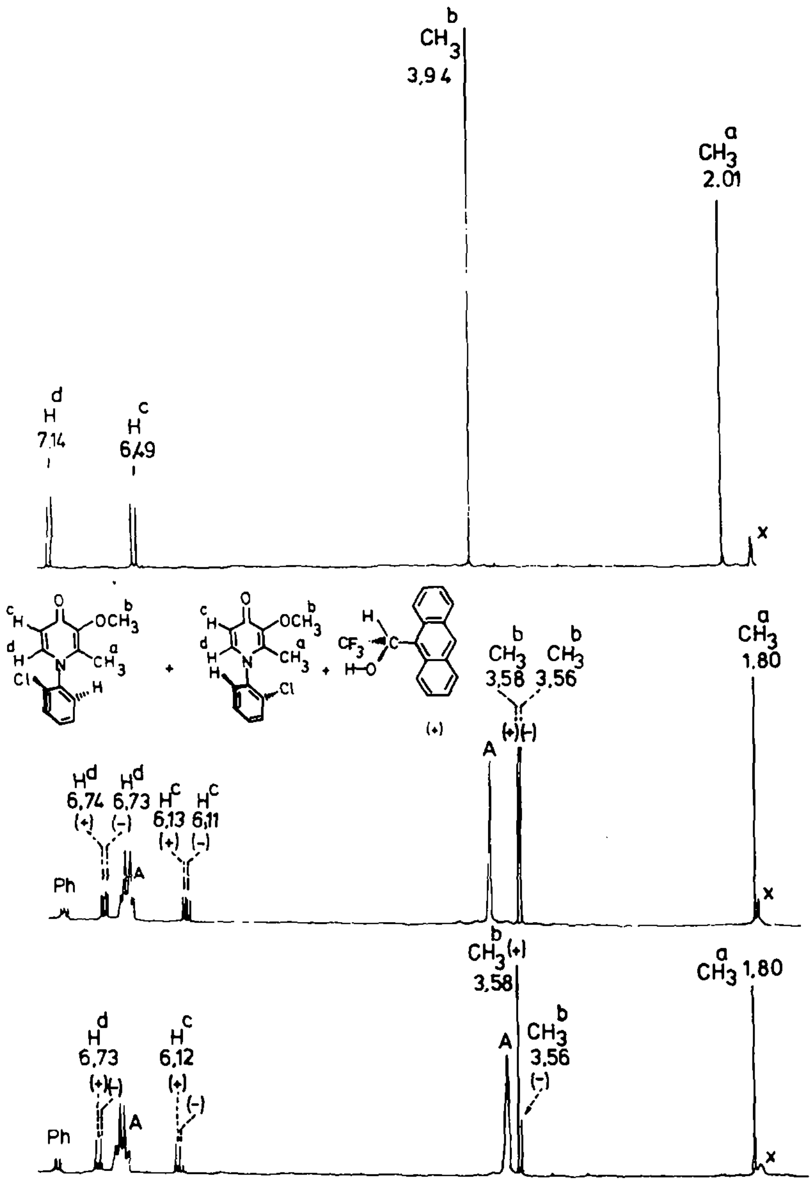


Fig. 2. Partial 250 MHz ^{1}H-PFT NMR of (±)-1 (top), (±)-1 in the presence of 8.63 equiv. of (+)-1-(9-anthryl)-2,2,2-trifluoroethanol (centre) and (±)-1 in the presence of 8.65 equiv. of (+)-1-(9-anthryl)-2,2,2-trifluoroethanol (bottom) in CDCl$_3$ at 23°. According to computer simulation[9] of the two CH$_3^b$ signals of a large-scale spectrum, the enantiomeric purity of (+)-1 was 56 ± 2%. Numbers are δ-values. A: Signals of auxiliary; Ph: part of phenyl absorption; X: probably absorption of trace of water.

two Me^b signals of the enantiomers. P-values and specific rotations resulted in $[\alpha]_{436}^{25} = 81 \pm 7$ and $[\alpha]_{365}^{25} = 228 \pm 10°$ ml g^{-1} dm^{-1} for the pure enantiomers of (+)-1 and (+)-2, respectively. The determination of P of (±)-4 and (±)-5 by ^{1}H-NMR or LC[5] was not successful because of insufficient enrichments and low specific rotations of the enantiomers.

Barriers to partial rotation about the C—N *bond*

The barriers were determined by thermal racemization (Table 1). Kinetics of first order were followed by polarimetry during 2–4 half-lives; the final angle of rotation was zero. In the case of 3 and 4, a racemization method without *preparative* enrichment proved to be efficient. An LC run of the racemate was stopped when the polarimetric detection was high. The polarimeter cell now contained the *solution* of an enriched enantiomer which was directly used for the measurement of racemization.

Compound 5 could not be racemized in diglyme even at 157°. Higher temperatures were not applied because of decomposition at 160°. The highest temp of the experiment permitted to calculate a lower limit of 134 kJ mol^{-1} for $\Delta G^{\ddagger}$ (Table 1). A similar limit of 100 kJ mol^{-1}[10] was obtained for the prochiral pyridone 6. In the presence of (+)-1-(9-anthryl)-2,2,2-trifluoroethanol, 6 showed *two* ^{1}H-NMR signals for the Me groups of the phenyl ring which did not coalesce at 140°. Compounds 5 and 6 owe their high barriers to

Table 1. Barriers to partial rotation about the C—N bond (cf. Scheme 1)

	Solvent	T (°)	$t_{0.5}$ (min)	10^5k (sec^{-1})	λ* (nm)	$\Delta G^\ddagger$† (kJ mol^{-1})
(−)-**1**	Diglyme	65.7±0.2	63.8±1.9	9.04	365	109.6±0.2
(+)-**2**	Diglyme	71.6±0.5	57.9±0.6	9.98	436	111.2±0.2
(−)-**3**	EtOH–H_2O (96:4)	24.8±0.5	20.7±0.5	27.9	365	93.2±0.4§
(+)-**4**	Diglyme	24.6±0.3	35.3±0.3	16.3	436	94.4±0.1
(+)-**4**	EtOH–H_2O (96:4)	23.1±0.2	202±6	2.85	546	98.3±0.1§
(+)-**5**	Diglyme	> 157	> 12	< 48.1	365	> 134‖

* Wavelength at which thermal racemization was monitored by the angle of rotation.

† Calculated by means of a computer[9a] program.

§ Obtained without *preparative* enrichment of enantiomers. Instead, the *solution* of an enriched enantiomer was used which was present in the polarimeter cell after stopping an LC run (see text).

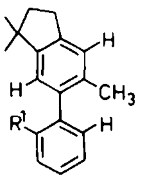
‖ No racemization was observed between 50 and 157°; lower limit for the barrier.

the presence of three interacting non-H substituents. This is also true for N-aryl-4,6-dimethyl-2(1H)-pyrimidinones and -thiones[3] as well as for N-aryl-2-methyl-4(3H)-quinazolinones.[1,2,5,11]

The $\Delta G^\ddagger$ of **4** in diglyme is increased by 3.9 kJ mol^{-1} when EtOH–H_2O (96:4) is chosen as solvent (Table 1), apparently *via* H-bonding.[6] If this value is applied to the barrier of **3**, measured in EtOH–H_2O (96:4), the following $\Delta G^\ddagger$-value in diglyme is estimated:

Compound	R^1 (R^2 = H)	$\Delta G^\ddagger$, diglyme (kJ mol^{-1})
3	CN	89.3
4	OCH_3	94.4±0.1
1	Cl	109.6±0.2
2	CH_3	111.2±0.2

These barriers may be compared qualitatively in spite of the somewhat different temperatures (Table 1) of racemization; even a moderately negative $\Delta S^\ddagger$ would not cause essential changes. The order and relative magnitudes of the above $\Delta G^\ddagger$-values are very close to the results for corresponding biphenyls[12] which enantiomerize *via* transition state **7**. Our pyridones **1**–**4** enantiomerize *via* **8** but the above absolute values of their barriers are roughly 30 kJ mol^{-1} higher than the ones of corresponding biphenyls. Two factors are responsible for this difference: (1) The buttressing effects exerted on the interacting groups are somewhat different in **7** and **8**. (2) The inter-ring C—N bond in **8** is shorter than the corresponding C—C bond in **7**, thus placing the interacting groups in **8** more closely together.[13] Contrary to biphenyls with two interacting non-H substituents, these two factors allow for the separability of the corresponding N-aryl-4-pyridone enantiomers at room temperature.



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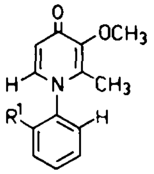

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R^1=Cl, CH_3, CN, OCH_3

EXPERIMENTAL

M.ps were determined on an Original Kofler Mikroheiztisch (Reichert, Wien) and are not corrected. IR spectra were recorded on a Perkin–Elmer 297 Infracord

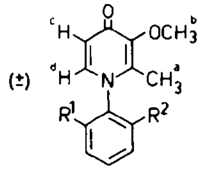
Table 2. Analytical and spectroscopic data

	Formula	M.p. (°)	Anal. C	Calc. (%) H	Found (%) N	$\nu_{C=O}$ (cm^{-1})*	λ_{max} (log ε) (nm)†
1	$C_{13}H_{12}ClNO_2$	122–123	62.53	4.84	5.61	1625 (s)	276 (4.38)
			62.39	4.85	5.85		
2	$C_{14}H_{15}NO_2 \times 1.5H_2O$	134–136	65.61	7.08	5.47	1620 (s)	275 (4.30)
			65.25	7.26	—		
3	$C_{14}H_{12}N_2O_2$	156–157	69.99	5.03	11.66	1625 (s)	280 (4.52)
			69.71	4.97	11.84		
4	$C_{14}H_{15}NO_3$	149–151	68.56	6.16	5.71	1620 (s)	282 (4.31)
			68.24	6.23	5.41		
5	$C_{14}H_{14}ClNO_2$	113–114	63.76	5.35	5.31	1625 (s)	276 (4.16)
			63.71	5.26	5.15		
6	$C_{15}H_{17}NO_2 \times 1H_2O$	142–143	68.94	7.33	5.36	1627 (s)	273 (4.35)
			69.02	7.59	5.42		

* In KBr.

† In methanol.

Table 3. ^{1}H-NMR δ and J-values ($CDCl_3$, 22°)



	R^1	R^2	a	b	c	d	Phenyl
1	Cl	H	2.02	3.93	6.47 J = 7.6 Hz	7.15 J = 7.6 Hz	7.35–7.60
2	CH_3 2.08	H	1.98	3.94	6.48 J = 7.4 Hz	7.16 J = 7.4 Hz	7.22–7.41
3	CN	H	2.07	3.94	6.50 J = 7.7 Hz	7.23 J = 7.7 Hz	7.31–7.95
4	OCH_3 3.83	H	2.01	3.92	6.45 J = 7.6 Hz	7.15 J = 7.6 Hz	6.99–7.58
5	CH_3 2.12	Cl	1.97	3.94	6.55 J = 7.6 Hz	7.08 J = 7.6 Hz	7.31–7.44
6	CH_3 2.05	CH_3 2.05	1.93	3.95	6.53 J = 7.4 Hz	7.08 J = 7.4 Hz	7.17–7.36

Table 4. Properties of enriched enantiomers

	M.p. (°)	$[\alpha]^{25}$ (° ml g^{-1} dm^{-1})	c (g l^{-1})	λ (nm)	Solvent
(+)-**1**	126–128	+45.1 ± 2.2*	3.1	436	CH_2Cl_2
(−)-**1**	126–128	−14.6 ± 0.7	8.7		
(+)-**2**	131–132	+54.8 ± 2.3†	3.1	365	acetone
(−)-**2**	136–137	−24.5 ± 0.9	8.6		
(+)-**5**	119.5–127	+16 ± 1‡	2.5	365	$CHCl_3$
(−)-**5**	119–120	−9 ± 1‡	3.4		

* Enantiomeric purity 56 ± 2%.

† Enantiomeric purity 24 ± 2%.

‡ The enrichment was too low for determination of enantiomeric purity.

Spectrophotometer. UV spectra were taken on a Hitachi–Perkin–Elmer 124 spectrophotometer. ^{1}H-NMR spectra were recorded on Jeol FX, 90 Ω (PFT mode, 8 K data points, 90 MHz) and Bruker WH 250 (PFT mode, 32 K data points, 250 MHz) spectrometers. (+)-1-(9-Anthryl)-2,2,2-trifluoroethanol was purchased from Ega-Chemie, Steinheim/Albuch. Elemental analyses were performed by Central Analytical Service, Institute "Ruder Bošković", Zagreb. Specific rotations were measured by means of a Perkin–Elmer 241 polarimeter. The details of chromatography and racemization have been described.[14]

3-Methoxy-2-methyl-4-pyrone was obtained by methylation of 3-hydroxy-2-methyl-4-pyrone with dimethyl sulphate according to the lit.[15] After the reaction was over, the product was left overnight in the refrigerator. The unreacted starting compound was removed by extraction with ether. The water layer was re-extracted with $CHCl_3$. The combined extracts were dried over $MgSO_4$. After the solvents were removed by evaporation, the product was purified by distillation under reduced pressure, b.p. 117–119°/17 Torr (78–79°/4 Torr).[16]

N-Aryl-3-methoxy-2-methyl-4-pyridones **1–6** were prepared according to the following general procedure.[7] A mixture of 3-methoxy-2-methyl-4-pyrone (0.016 mol) and the appropriate aniline (0.018 mol) in 20 ml of MeOH–water (1 : 1) was heated in a thick-walled sealed glass tube at 150–160° for 48 hr. After removing the solvent by evaporation under reduced pressure, the oily product was purified by repeated column chromatography on silica gel (0.063–0.200 mm) with EtOAc–acetone (1 : 1) as an eluent. Two recrystallizations from EtOAc yielded colourless crystals. The final purification for separations of enantiomers and spectroscopic measurements were achieved by vacuum sublimation at 150–190°/0.1 Torr. The yields varied from 25–30%.[17] Specific data for the pyridones and the enriched enantiomers are given in Tables 2–4.

Acknowledgements—This work was supported by the Fonds der Chemischen Industrie (Federal Republic of Germany) and the Selfmanagement Communities for Scientific Work of SR Croatia (Yugoslavia). We are grateful to Dr. T. Burgemeister and Mrs. U. Fritzsche for the ^{1}H-NMR spectra.

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