Journal of Chromatography, 387 (1987) 313–321
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 19 071

DIRECT LIQUID CHROMATOGRAPHIC SEPARATION OF PHTHALIDE ENANTIOMERS

WILLIAM H. PIRKLE* and THOMAS J. SOWIN
School of Chemical Sciences, University of Illinois, Urbana, IL 61801 (U.S.A.)
(Received September 4th, 1986)

SUMMARY

The enantiomers of a series of 3-substituted phthalides (3-substituted-1-(3H)-isobenzofuranones) have been separated by high-performance liquid chromatography on commercially available chiral stationary phases derived from (*S*)-leucine and (*R*)-phenylglycine. Chromatographic data and a chiral recognition model are presented for the separation of phthalide enantiomers on these chiral phases. Assignment of elution orders based on the *a priori* model proposed are consistent with those ultimately determined by independent chemical and spectroscopic means.

INTRODUCTION

In our continuing investigation into mechanisms by which enantiomers are chromatographically separated on a series of chiral stationary phases (CSPs) developed in our laboratory, we became interested in the separation of type 1 3-substituted phthalides. Several phthalides occur naturally[1,2] while others have been the subject of several asymmetric syntheses[3–5] the most significant of which are those of Meyers *et al.*[6]. Although the absolute configurations of a few phthalides have been determined by chemical and/or spectroscopic means[3–6], no general methods for resolving or assigning absolute configurations to phthalides have been advanced. Chromatographic separations of enantiomers yield useful quantities of pure enantiomers[7] and offer a means for accurate determination of enantiomeric purities as well. In addition, absolute configurations may be inferred from observed elution orders if the details of the chiral recognition process are known[8]. Hence, a chromatographic technique for the facile separation of phthalide enantiomers and an understanding of the mechanism whereby the separations occur would be of general interest and utility.

In this vein, a diverse series of phthalides and phthalide analogues was prepared and the chromatographic behavior of these compounds was studied on CSPs derived from (*R*)-phenylglycine and (*S*)-leucine. The chromatographically derived data have been utilized in the elucidation and substantiation of the phthalide chiral recognition process.

0021-9673/87/$03.50

EXPERIMENTAL

Chromatography was performed using an Altex 100A pump, Altex 210 injector, and an Altex Model 152 dual-wavelength (254 and 280 nm) detector. Either Kipp and Zonen BD41 or Altex Model C-RIA integrating recorders were used. A Rudolph Autopol III polarimeter containing a 20-cm flow cell was used in series with the ultraviolet detector to monitor simultaneously the sign of $[\alpha]_D$ as the enantiomers eluted. Regis covalent (*R*)-phenylglycine Pirkle 1-A and Baker covalent (*S*)-leucine columns (250 × 4.6 mm) were used to generate the data in the tables. Melting points were obtained using a Buchi apparatus and are uncorrected. ^{1}H NMR spectra were obtained on Varian XL-200 (200 MHz), Nicolet NT-360 (360 MHz) or GE QE-300 (300 MHz) spectrometers using tetramethylsilane as an internal reference. IR spectra were recorded on either an IBM IR-32 Fourier transform infrared (FT-IR) or a Nicolet 7000 FT-IR spectrometer.

New compounds in the tables were fully characterized by melting point, NMR and IR spectroscopy, and either elemental analyses within 0.40% of expected values for C, H, and S or, for compounds 1d, 1j, 1l, 1p, 1r, 1s and 5a, the proper molecular weight as determined by high-resolution mass spectrometry. Phthalide 1a, enriched in the (*S*)-enantiomer, was obtained from A. I. Meyers (Colorado State University).

The phthalides in Table I and compounds 3a–b, 4a and 5a were synthesized by either of the two procedures described herein. The thiono phthalide derivatives, 2a–d, were prepared from the corresponding phthalide using the dimer of 4-methoxyphenylthiophosphine sulfide as described by Scheibye *et al.*[11]. Characterization data for most of the compounds presented in the tables is being described elsewhere. However, data is provided herein for the compounds to be presented only in this paper.

General synthesis of phthalides

Procedure A[12]. To a stirred solution of *o*-bromobenzoic acid in anhydrous tetrahydrofuran (THF) at −100°C and maintained under a nitrogen atmosphere was slowly added two equivalents of *n*-butyllithium (via syringe) over a 20-min period. The solution was warmed to −78°C and the appropriate ketone or aldehyde, dissolved in a small volume of THF, was slowly added via syringe and the solution was then allowed to warm to room temperature over a 1-h period. The reaction mixture was poured into water and the mixture washed with diethyl ether. The aqueous phase was isolated, acidified to pH 1 with concentrated aqueous hydrochloric acid and extracted with diethyl ether. The ether layer was isolated, washed with cold 5% aqueous sodium hydroxide solution, water, and dried over magnesium sulfate. The ether was removed *in vacuo* to give the desired phthalide. Purification, if needed, was achieved by flash chromatography on silica or recrystallization from ethanol.

Procedure B. To a stirred solution of the appropriate keto-acid in anhydrous THF cooled to −78°C and maintained under a nitrogen atmosphere was slowly added either sodium borohydride or the desired Grignard or lithium reagent. The solution was warmed to 25°C (over a 1-h period) and quenched by addition to water. The reaction was then worked up as in procedure A.

3-(4′-Methoxyphenyl)-3-methylphthalide (1b). 1b was obtained in 45% yield by procedure A using 4-methoxyacetophenone and isolated as a white solid. m.p.

60–61°C. Analytical: calculated for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.38; H, 5.43; ^1H NMR (C^2HCl_3) δ 2.02 (s, 3H), 3.73 (s, 3H), 6.6–7.8 (m, 8H). IR ($CHCl_3$) 3100–3000, 1757 (C = O), 1512, 1181, 1099 cm^{-1}.

3-(9′-Anthryl)phthalide (1c). 1c was obtained by procedure A using 9-anthraldehyde in 11% yield and isolated as a yellow solid. m.p. 140–142°C. Analytical: calculated for $C_{22}H_{14}O_2$: C, 85.13; H, 4.56. Found: C, 84.88; H, 4.81. ^1H NMR (C^2HCl_3) δ 6.92–7.51 (m, 8H), 7.84–8.21 (m, 4H), 8.51 (s, 1H). IR (KBr) 3600–3200, 3100, 1761 (C = O), 1284, 1089, 759, 720, 712 cm^{-1}.

3-(10′-Methoxy-9′-anthryl)phthalide (1d). 1d was obtained in 60% yield by procedure A using 10-methoxy-9-anthraldehyde and isolated as a yellow solid. m.p. 182–187°C. High-resolution mass spectrum, calculated for $C_{23}H_{14}O_3$: 340.1099. Found: 340.1103; ^1HNMR (C^2HCl_3) δ 4.12 (s, 3H), 7.00–8.51 (m, 13H). IR ($CHCl_3$) 3100–2800, 1762 (C = O), 1286, 1095, 1069, 969 cm^{-1}.

3-(1′-Naphthyl)hexahydrophthalide (3a). 3a was obtained in 30% yield by procedure B using 1′-naphthoyl-2-cyclohexanecarboxylic acid and sodium borohydride and isolated as a white solid. m.p. 153–155°C. Analytical: calculated for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.91; H, 7.06. ^1H NMR (C^2HCl_3) δ 1.21–1.78 (m, 6H). 1.88–2.12 (m, 2H), 2.45–2.60 (m, 1H), 2.65–2.80 (m, 1H), 5.34 (d, 1H, J = 3.18 Hz), 7.38–7.87 (m, 7H). IR (KBr) 3100–2850, 1767 (C = O), 1294, 1240, 1176 cm^{-1}.

5(1′-Naphthyl)-5-methylbutyrolactone (4a). 4a was obtained in 22% yield by procedure B using 3-(1′-naphthoyl)propionic acid and methylmagnesium bromide and isolated as as slightly yellowish oil. Analytical: calculated for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.51; H, 6.36. ^1H NMR (C^2HCl_3) δ 1.99 (s, 3H), 2.44–2.91 (m, 4H), 7.38–8.10 (m, 7H), IR (neat) 3100–2850, 1782 (C = O), 1450, 1250, 1209, 1138, 1090, 943, 920 cm^{-1}.

1,3-Dihydro-1-(1′-naphthyl)isobenzofuran (5a). 5a was obtained by a modified version of procedure B using 1′-naphthoyl-2-benzoic acid and sodium borohydride. Compound 5a became the major product rather than the phthalide 1e when the reaction mixture was poured into 5% hydrochloric acid solution and stirred overnight before being worked up. Thus, 5a was isolated as a yellow oil in 65% yield. High-resolution mass spectrum calculated for $C_{18}H_{14}O$: 246.1051. Found: 246.1048. ^1H NMR (C^2HCl_3) δ 5.24–5.41 (m, 2H), 6.96 (s, 1H), 7.07–7.51 (m, 8H), 7.78–7.90 (m, 2H), 8.18–8.23 (m, 1H). IR (neat) 3100–2800, 1447, 1236, 1087, 954 cm^{-1}.

RESULTS AND DISCUSSION

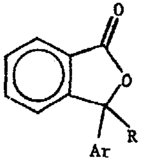
The high-performance liquid chromatography (HPLC) columns used in this study contain CSPs derived from the 3,5-dinitrobenzamides of either (*R*)-phenylglycine or (*S*)-leucine covalently bonded to 5-μm spherical silica particles. Ionically bonded CSPs of this type afford similar results but with somewhat lower separability factors. Such columns are now commercially available*.

---

* Columns containing the phenylglycine and leucine-derived CSPs described herein are available from Regis Chemical (Morton Grove, IL, U.S.A.), and J. T. Baker (Phillipsburg, NJ, U.S.A.), Phenylglycine-derived CSP is also available from Sumitomo Chemical (Osaka, Japan).

TABLE I

RESOLUTION OF RACEMIC PHTHALIDES ON CHIRAL STATIONARY PHASES



(1)

Compound (ref.)	Ar	R	CSP					
			(R)-N-3,5-Dinitrobenzoylphenylglycine			(S)-N-3,5-Dinitrobenzoylleucine		
			α^*	$k_1'^{**}$	First eluting	α^*	$k_1'^{**}$	First eluting
1a	Phenyl	CH_2CH_3	1.00	1.87^{***}	–	1.03	4.35^{***}	(–)-*R*
1b	4-Methoxyphenyl	CH_3	1.00	3.50	–	1.06	4.43	(–)
1c	9-Anthryl	H	1.05	7.71	(–)	1.07	9.21	(+)
1d	10-Methoxy-9-anthryl	H	1.05	8.14	(–)	1.07	9.14	(+)
1e (9)	1-Naphthyl	H	1.09	1.95	(+)-*S*	1.19	5.86	(–)-*R*
1f (10)	1-Naphthyl	CH_3	1.57	4.00	(–)-*S*	2.03	5.71	(+)-*R*
1g	1-Naphthyl	CF_3	1.15	1.43	(–)	1.30	1.43	(+)
1h	1-[6,7-$(CH_3)_2$]-Naphthyl	CH_3	2.03	4.71	(–)	2.84	6.29	(+)
1i	1-[6,7-$(CH_3)_2$]-Naphthyl	$CH(CH_3)_2$	2.89	2.57	(–)	4.39	3.29	(+)
1j	1-[6,7-$(CH_3)_2$]-Naphthyl	cyclohexyl	3.72	2.57	(–)	5.19	4.21	(+)
1k	1-[3,7-$(CH_3)_2$]-Naphthyl	CH_3	2.17	3.29	(–)	2.84	5.57	(+)
1l	1-[3,7-$(CH_3)_2$]-Naphthyl	phenyl	3.05	2.71	(–)	4.52	3.57	(+)
1m	1-[4,7-$(CH_3)_2$]-Naphthyl	H	1.15	6.57	(+)	1.36	7.14	(–)
1n	1-[4,7-$(CH_3)_2$]-Naphthyl	CH_3	2.06	4.61	(–)-*S*	2.70	5.50	(+)-*R*
1o	1-[4,7-$(CH_3)_2$]-Naphthyl	$(CH_2)_3CH_3$	2.39	2.57	(–)	3.96	3.57	(+)
1p	1-[4,7$(CH_3)_2$]-Naphthyl	$(CH_2)_7CH_3$	2.55	2.07	(–)	4.09	3.00	(+)
1q	1-[4,7-$(CH_3)_2$]-Naphthyl	$C{\equiv}C\text{-}(CH_2)_5CH_3$	2.42	2.71	(–)	3.80	5.00	(+)
1r	1-[4,7-$(CH_3)_2$]-Naphthyl	$(CH_2)_9CHCH_2$	2.75	2.00	(–)	4.37	3.50	(+)
1s	1-[2,3-$(CH_3)_2$]-Naphthyl	CH_3	1.00	3.63	–	1.00	3.19	–
1t	2-Naphthyl	H	1.04	$8.50^{\S}$	(+)-*S*	1.00	$7.75^{\S}$	–
1u	2-Naphthyl	CH_3	1.03	$6.06^{\S}$	(+)-*S*	1.02	$5.19^{\S}$	(–)-*R*
1v	2-[6,7-$(CH_3)_2$]-Naphthyl	$CH(CH_3)_2$	1.00	2.43	–	1.17	2.07	(–)

* Chromatographic separation factor.

** Unless otherwise indicated, mobile phase was 10% 2-propanol in hexane.

*** Mobile phase was 1% 2-propanol in hexane.

§ Mobile phase was 5% 2-propanol in hexane.

Table I presents the relevant data obtained from chromatography of a series of 3-substituted phthalides on the aforementioned CSPs. Examination of Table I reveals that the 1-naphthylphthalides 1e–s (excepting 1s) resolve substantially better than the phenyl (1a–b), 2-naphthyl (1t–v), and 9-anthryl (1b–c) substituted phthalides. The latter three classes of phthalides exhibit only modest separation factors for the enantiomers. In each case in which resolution is observed, the elution orders from the two CSPs differ owing to the difference in absolute configuration of the two CSPs. The (*S*)-leucine-derived CSP generally affords greater separation factors than the (*R*)-phenylglycine-derived CSP. An increase in the steric bulk or alkyl chain length of the R-group in the 1-naphthyl substituted phthalides greatly increases the magnitude of the separation factors of the enantiomers. Fig. 1 illustrates the facility with which the enantiomers of 3-(1-naphthyl and 1-dimethylnaphthyl)-3-alkylphthalides are separated on the CSPs. The extent of separation of these phthalide enantiomers makes preparative resolutions facile. For example, we have previously reported the gram scale resolution of 1k using medium pressure liquid chromatography[13] and the preparative resolutions of 1k and 1o by flash chromatography[14]. Moreover, the phthalides which afford the highest enantiomeric separation factors, thus indicating a high degree of chiral recognition between analyte and CSP, become of interest as possible candidates for incorporation into phthalide-derived CSPs[15].

The absolute configurations of phthalides 1e, 1f, 1n, 1t and 1u were determined by chemical and spectroscopic techniques, the details of which will be presented in a synthetically oriented journal. The configuration of 1a had been previously determined[6]. Circular dichroic spectroscopic analysis indicated, by correlation with the CD spectra of the configurationally known phthalides, that all the 1-naphthyl-, 2-naphthyl- and phenyl-substituted phthalides in Table I elute in the same order with the (*S*)-phthalide enantiomer being least retained on the (*R*)-phenylglycine CSP and the (*R*)-enantiomer least retained on the (*S*)-leucine CSP. Although the absolute

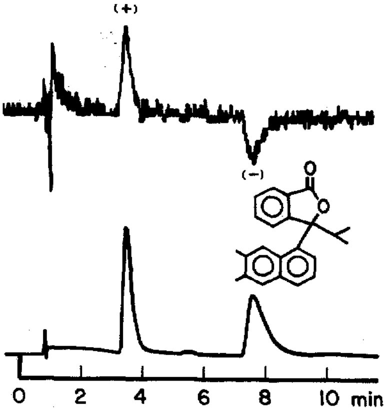


Fig. 1. Analytical scale resolution of racemic phthalide 1i on a 250 × 4.6 mm covalent 3,5-dinitrobenzoylleucine column. Shown is the polarimetric tracing obtained using a Rudolph Autopol III digital polarimeter containing a 20-cm flow cell used in series with the ultraviolet detector to simultaneously monitor the sign of $[\alpha]_D$ as the enantiomers eluted. Mobile phase: 10% 2-propanol in hexane. Flow-rate: 2 ml/min.

configuration of the 9-anthryl substituted phthalides were not determined, we expect them to have the same elution order as the rest of the phthalides in Table I.

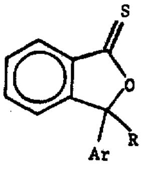
Table II presents the results of the chromatography of various phthalide analogues on the CSPs. These compounds resemble phthalides except for some structural alteration from the basic phthalide structure. In general, these structural changes cause a decrease in the magnitude of α relative to that of the corresponding phthalide. For example, the phthalide 1-thiono derivatives 2a–d, although eluting in the same order as the corresponding phthalides 1e, 1f, 1n, 1t, 1u respectively, exhibit lower α values, especially for the 1-naphthyl derivatives 1e, 1f, 1n.

Chiral recognition rationale

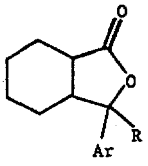
Chiral recognition of a phthalide enantiomer by the CSP can only occur if there are at least three simultaneous interactions, at least one of which is stereochemically dependent, between the CSP and the "recognized" phthalide enantiomer. Illustrated in Fig. 2a is the chiral recognition mechanism that we feel most suitable to account for the separation of the enantiomers of 1-naphthyl substituted phthalides. The phthalide, based on examination of molecular models, is shown in the confor-

TABLE II

RESOLUTION OF PHTHALIDE ANALOGUES ON CHIRAL STATIONARY PHASES

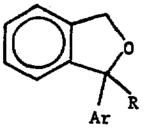


2



3

4



5

Compound	Ar	R	CSP					
			(R)-N-3,5-Dinitrobenzoyl-phenylglycine			(S)-N-3,5-Dinitrobenzoyl-leucine		
			α*	k'_1**	First eluting	α*	k'_1**	First eluting
2a	1-Naphthyl	H	1.09	3.50	(+)	1.15	1.50	(−)
2b	1-Naphthyl	CH_3	1.21	2.38	(−)	1.54	1.63	(+)
2c	1-[4,7-$(CH_3)_2$]-Naphthyl	CH_3	1.43	1.75	(−)	1.84	1.63	(+)
2d	2-Naphthyl	H	1.06	3.25	(+)	1.00	2.50	–
2e	2-Naphthyl	CH_3	1.01	1.50	(+)	1.01	1.38	(−)
3a	1-Naphthyl	H	1.00	3.88	–	1.00	3.12	–
3b	1-Naphthyl	CH_3	1.00	2.62	–	1.13	2.00	(+)
4a	1-Naphthyl	CH_3	1.12	2.63	(+)	1.37	4.38	(−)
5a	1-Naphthyl	H	1.00	1.00	–	1.00	1.54	–

* Enantiomeric separation factor.

** Mobile phase was 5% 2-propanol in hexane.

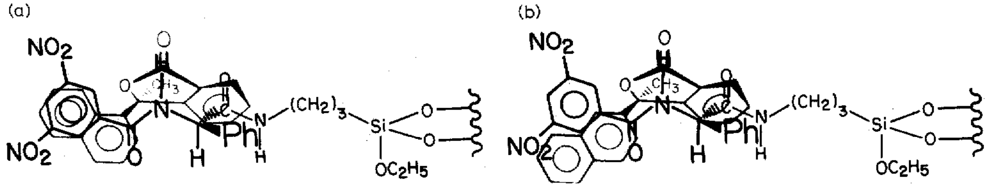


Fig. 2. Chiral recognition model for the selective retention of one 1-naphthyl and 2-naphthyl-substituted phthalide enantiomer (respectively) by the chiral stationary phase. In each case the depicted configurations lead to the most stable diastereomeric absorbate. Comparison of a and b illustrates the difference in π-overlap of the 1-naphthyl and 2-naphthyl systems with the 3,5-dinitrobenzoyl group of the chiral stationary phase, thus accounting for the diminished chiral recognition of the 2-naphthyl-substituted phthalides.

mation presumed to be important for chiral recognition. The (*R*)-phenylglycine CSP is shown in the conformation similar to the solution and solid-state conformations preferentially populated by amides of primary amines having a single α-hydrogen. This conformation has been suggested previously to be important to chiral recognition[16].

We envision three simultaneous interactions for the relative configurations of phthalide and CSP shown in Fig. 2a: (a) π–π bonding interaction between the 3,5-dinitrobenzoyl group of the CSP and the naphthyl group of the phthalide, (b) hydrogen bonding of the 3,5-dinitrobenzamide hydrogen and the carbonyl oxygen of the phthalide, (c) steric discrimination by the phthalide benzo ring between the smaller carboxamide group and the larger geminal phenyl group of the CSP.. In addition, there may be a slight bonding interaction between the positive end of the carboxamide dipole of the CSP and the phthalide benzo ring, thus further enhancing the effective size difference between the carboxamide and phenyl groups. Thus, the (*R*)-phthalide enantiomer depicted in Fig. 2a will be the last to elute from the (*R*)-phenylglycine CSP shown. The (*S*)-phthalide enantiomer, in order to achieve the first two described bonding interactions with the CSP, would have to approach from the other face of the CSP thereby thrusting the benzo ring of the phthalide against the bulky phenyl group of the CSP, thus forming a less stable diastereomeric absorbate. Therefore, the (*S*)-enantiomer will be first to elute from the (*R*)-phenylglycine CSP. The data presented in Table I is in full agreement with this model.

Increasing or decreasing the strength of the interactions important to chiral recognition should likewise increase or decrease the magnitude of α. The increased separability of the 1-dimethylnaphthyl substituted phthalides, as compared to the 1-naphthyl substituted phthalides, is attributed to the increased π-basicity of the dimethylnaphthyl system as well as the role the 7′-methyl group serves in restricting and orienting the conformation of the dimethylnaphthyl group relative to the phthalide ring system. The conformation thought to be most important to chiral recognition is shown in Fig. 2a. Similarly, an increase in the steric size or chain length of the 3-alkyl group increases the magnitude of α by helping to orient the 1-naphthyl system to the conformation favorable for chiral recognition. Additionally, the 3-alkyl substituent protects the "backside" of the phthalide molecule from interaction with CSP, an interaction which might lead to retention without chiral recognition. Dramatically illustrating the importance of the conformation of the 1-naphthyl system on chiral recognition is 1s. The dimethylnaphthyl group of 1s, due to steric interaction between the 2′-methyl of the naphthyl ring and the peri-hydrogen of the phthalide benzo ring, cannot achieve the conformation necessary for effective chiral recognition, thus rendering 1s unresolvable on the CSPs used herein. The decreased separability of 1g as compared to its methyl substituted analogue 1f, is attributed to the electron withdrawing properties of the trifluoromethyl group of 1g. The trifluoromethyl group inductively decreases the π-basicity of the naphthyl group and also removes electron density from the carbonyl oxygen (indicated by a 30 cm^{-1} increase in the IR carbonyl stretching frequency of 1g relative to 1f) thereby decreasing the strength of the bonding interactions and thus decreasing α and hastening elution.

The dramatic decline in separability of the 2-naphthyl-substituted phthalides 1t–v, compared to their 1-naphthyl analogues, is easily understood by comparison of Figs. 2a and 2b. The naphthyl group in the 1-naphthyl-substituted phthalides (Fig. 2a) lies directly over the 3,5-dinitrobenzoyl group of the CSP, thus providing an effective π–π interaction. However, the naphthyl group in the 2-naphthyl-substituted phthalides (Fig. 2b), while maintaining the other two described interactions with the CSP, lies askew of the 3,5-dinitrobenzoyl group of the CSP yielding a weaker π–π interaction and reducing chiral recognition. Similarly, the phenyl-substituted phthalides modest separability arises from the inability of the two π-systems to form a strong π–π bond. The 9-anthryl-substituted phthalides, although possessing increased π-basicity relative to the naphthyl systems, show only small α values due to steric interactions between the anthryl and benzo rings similar to those of 1s. Steric interaction between the peri-hydrogens on the anthryl and benzo rings must prevent the anthryl group from achieving the conformation necessary for an effective π–π interaction with the CSP. Although the separability of the 2-naphthyl-, phenyl- and 9-anthryl-substituted phthalides is reduced compared to the 1-naphthyl-substituted phthalides, their elution orders and chiral recognition mechanisms appear to be fundamentally the same.

Further validation of the phthalide chiral recognition mechanism is brought forth from the chromatographic behavior of structural variants of phthalides on the CSPs. The hastened elution and reduced chiral recognition of the phthalide 1-thiono derivatives 2a–e, compared to the analogous phthalides, is expected since the less electronegative sulfur forms a weaker hydrogen bond to the CSP. Moreover, total removal of hydrogen bonding capability by removal of the carbonyl, effectively eliminates chiral recognition and renders 5a unresolvable. The importance of the phthalide's benzo ring in chiral recognition is demonstrated by the separabilities of 3a–b and 4a. Saturation of the benzo ring results in almost complete loss of separability for 3a–b. However, the diminished separabilities of 3a–b may be in part due to the altered conformation of the 5-membered lactone rings as compared to the phthalides. Similarly, as 4a illustrates, removal of the benzo ring also results in decreased separability when compared to phthalide 1f.

ACKNOWLEDGEMENTS

Microanalyses were performed by J. Nemeth and associates (University of Illinois). Mass spectra were obtained by J. C. Cook and associates (University of Illinois). This work was financially supported by the National Science Foundation.

REFERENCES

1 D. H. R. Barton and J. X. de Vries, *J. Chem. Soc.*, (1963) 916.
2 M. Elander, K. Leander and B. Luning, *Acta Chem. Scand.*, 23 (1969) 2177.
3 M. N. Kolosov, A. I. Guevich and Yu. B. Shvestov, *Izv. Akad. Nauk SSSR, Otd. Khim Nauk.*, (1963) 701.
4 P. R. Jones and C. J. Jarboe, *Tetrahedron Lett.*, (1969) 1849.
5 M. Asami and T. Mukaiyama, *Chem. Lett.*, (1980) 17.
6 A. I. Meyers, M. A. Hanagan, L. M. Trefonas and R. J. Baker, *Tetrahedron*, 39 (1983) 1991.
7 W. H. Pirkle and J. M. Finn, *J. Org. Chem.*, 47 (1982) 4037.
8 W. H. Pirkle, J. M. Finn, B. C. Hamper, J. Schreiner and J. R. Pribish, in E. Eliel and S. Otsuka (Editors), *Asymmetric Reactions and Processes in Chemistry, No. 185*, American Chemical Society, Washington, DC, 1982.
9 M. S. Newman, *J. Org. Chem.*, 40 (1975) 2996.
10 M. S. Newman, *J. Am. Chem. Soc.*, 59 (1937) 1003.
11 S. Scheibye, J. Kristensen and S. O. Lawesson, *Tetrahedron*, 35 (1979) 1339.
12 W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, 39 (1974) 2051.
13 W. H. Pirkle and J. M. Finn, *J. Org. Chem.*, 47 (1982) 4037.
14 W. H. Pirkle, A. Tsipouras and T. J. Sowin, *J. Chromatogr.*, 319 (1985) 392.
15 W. H. Pirkle, in S. Ahuja (Editor), *Chromatography and Separation Chemistry: Advances and Developments* (*ACS Symposium Series*, No. 297), American Chemical Society, Washington, DC, 1986.
16 W. H. Pirkle, D. W. House and J. M. Finn, *J. Chromatogr.*, 192 (1980) 143.