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A Chiral Stationary Phase for the Facile Resolution of Amino Acids, Amino Alcohols, and Amines as the *N*-3,5-Dinitrobenzoyl Derivatives

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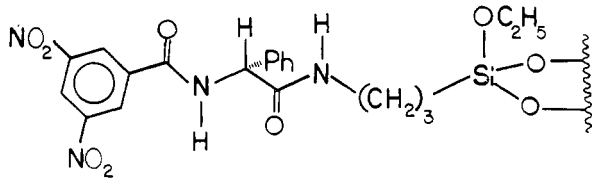
A chiral stationary phase derived from α-(6,7-dimethyl-1-naphthyl)isobutylamine is quite effective for the liquid chromatographic separation of the enantiomers of the *N*-3,5-dinitrobenzoyl derivatives of α-amino acids, their esters and amides, amino alcohols, and amines. For example, the chromatographic separation factor for the enantiomers of derivatized methyl phenylalanate is 4.73, the band shapes are excellent, and the resolution value is 16.5. Additionally, the 3,5-dinitrobenzoates of a number of secondary alcohols are resolvable on this chiral phase. An analogous stationary phase derived from α-(1-naphthyl)ethylamine performs less well for the amino acid ester derivatives but is superior for a few of the amine derivatives.

An earlier paper in this series describes[1] the chromatographic separation of the enantiomers of N-acylated 1-aryl-1-aminoalkanes on a chiral stationary phase (CSP), 1, derived from the 3,5-dinitrobenzamide of (*R*)-phenylglycine.[2] That study provided insight into the mechanism(s) of chiral recognition responsible for the observed separations. We herein show how such insight can be applied to the design of a 1-aryl-1-aminoalkane-derived CSP upon which the enantiomers of α-amino acids, the esters and amides thereof, amino alcohols, and amines, all as the 3,5-dinitrobenzamides, may be readily separated. This CSP also separates the enantiomers of a number of secondary alcohols as the 3,5-dinitrobenzoates.



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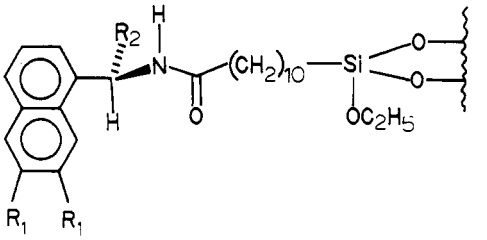
We have previously used the chromatographic separability of enantiomers on a given CSP as a gauge to judge how well a CSP derived from one of those enantiomers might work in a reciprocal fashion.[3] From the aforementioned study of N-acylated 1-aryl-1-aminoalkanes, it seemed likely that a structurally "optimized" (for chiral recognition) member of this series could be incorporated into useful "reciprocal" CSP on which the enantiomers of amines, amino acids, and amino alcohols could be separated, all as the *N*-3,5-dinitrobenzoyl derivatives. Our initial design for this reciprocal CSP was based on the premise that (a) it is desirable to utilize a 1-naphthyl-like system so as to take advantage of the conformational control provided by the peri hydrogen, (b) one may increase the π-basicity of the napthyl system through substitution with methyl groups, (c) the alkyl substituent on the chiral center should be bulky to help control conformation, and (d) the chiral moiety should be connected to the support by a reasonably lengthy and nonpolar arm. CSP **2** embodies all these features. The methyl groups in the 6,7-positions of the naphthyl system enhance π-basicity without interfering with the π–π interactions essential to chiral recognition.



2, $R_1 = CH_3$; R_2 = isopropyl
3, R_1 = H; $R_2 = CH_3$

Amides of 1-(1-naphthyl)ethylamine have been used previously as CSPs. The lauroylamide was used by Gil-Av,

(1) Pirkle, W. H.; Welch, C. J.; Hyun, M. H. *J. Org Chem.* in press.
(2) The preparation of this chiral phase has been described[3] and columns containing this material are available from Regis Chemical Co. (8210 Austin Ave., Morton Grove, IL 60053) and J. T. Baker Chemical Co. (222 Red School Lane, Phillipsburg NJ 08865).
(3) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, *192*, 143.

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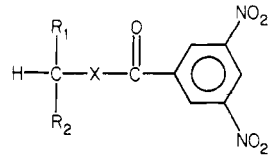
Table I. Separation of Enantiomers of CSP 2 and CSP 3



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		CSP 2			CSP 3		
R_1	R_2	α[a]	k'_1[b]	conf[c]	α[a]	k'_1[b]	conf[c]
		X = NH					
CH_3	$COOCH_3$	3.34	6.7 (2)	*R*	2.02	10.6 (1)	*R*
i-C_3H_7	$COOCH_3$	4.30	6.3 (2)	*R*	2.69	7.1 (1)	*R*
i-C_4H_9	$COOCH_3$	3.84	7.0 (2)	*R*	2.38	7.5 (1)	*R*
t-C_4H_9	$COOCH_3$	3.42	5.1 (2)	*R*	2.50	3.9 (1)	*R*
phenyl	$COOCH_3$	2.46	9.8 (2)	*R*	1.22	17.8 (1)	*R*
benzyl	$COOCH_3$	4.73	8.7 (2)	*R*	1.93	18.5 (1)	*R*
4-F-benzyl	$COOCH_3$	5.20	7.3 (2)		2.17	16.4 (1)	
α-naphthyl	$COOCH_3$	2.27	7.8 (2)		1.56	11.6 (1)	
CH_3	CONH-*n*-Bu	1.29	3.3 (1)	*R*	1.50	2.5 (1)	*R*
i-C_3H_7	CONH-*n*-Bu	1.98	1.2 (2)	*R*	2.09	1.0 (1)	*R*
i-C_4H_9	CONH-*n*-Bu	1.54	1.7 (1)	*R*	1.77	1.2 (1)	*R*
phenyl	CONH-*n*-Bu	1.06	4.6 (1)	*S*	1.50	3.3 (1)	*S*
benzyl	CONH-*n*-Bu	2.34	1.7 (1)	*R*	1.51	2.3 (1)	*R*
C_2H_5	CH_2OH	1.18	4.3 (2)	*R*	1.26	8.1 (1)	*R*
C_2H_5	CH_2OCH_3	1.67	6.4 (2)	*R*	1.79	10.3 (1)	*R*
i-C_3H_7	CH_2OH	1.47	3.0 (2)	*R*	1.36	5.9 (1)	*R*
phenyl	CH_3	1.65	9.6 (2)	*R*	2.09	6.9 (2)	*R*
phenyl	*i*-C_3H_7	3.02	11.9 (2)	*R*	2.59	8.1 (2)	*R*
benzyl	CH_3	1.39	5.2 (2)	*S*	1.12	5.4 (2)	*R*
n-C_4H_9	CH_3	1.69	4.5 (2)		1.17	11.6 (1)	
n-C_5H_{11}	CH_3	1.14	4.5 (2)		NR[d]		
		X = O					
phenyl	CH_3	1.08	1.1 (3)		1.04	2.2 (4)	
phenyl	*t*-C_4H_9	1.27	0.7 (3)		1.09	1.2 (4)	
phenyl	*n*-C_4H_9	1.25	0.7 (3)		1.10	1.3 (4)	
phenyl	cyclopropyl	1.13	1.1 (3)		1.07	1.9 (4)	
4-Cl-phenyl	CH_3	1.14	1.6 (3)		1.04	3.0 (4)	
9-anthryl	CH_3	1.52	2.7 (3)		1.19	4.9 (4)	

[a] Chromatographic separability factor. [b] Capacity factor for the first eluted enantiomer. Mobile phase is noted by the number in the parenthesis as follows: (1) 10% isopropyl alcohol in *n*-hexane; (2) 20% isopropyl alcohol in *n*-hexane; (3) 1% isopropyl alcohol in *n*-hexane; (4) 0.2% isopropyl alcohol in *n*-hexane. [c] Absolute configuration of the second eluted enantiomer. Elution orders have not yet been established for those compounds for which no entry is present. [d] No resolution.

Weinstein, and Feibush as a stationary phase for gas chromatography.[4] More recently, Oi, Nagase, and Doi have prepared CSPs derived from the terephthamide and succinamide of this amine and used them for HPLC separation of the enantiomers of the *N*-3,5-dinitrobenzoyl derivatives of amines and α-amino acid esters or amides.[5] The synthetic approach to CSP 2 involves Friedel–Crafts acylation of 2,3-dimethylnaphthlene with isobutyryl chloride, chromatographic purification of the α-isomer (CH_2Cl_2–silica), and reductive amination of this ketone (sodium cyanoborohydride, ammonium acetate, methanol at reflux overnight). The resultant racemic amine was acylated with 10-undecenoyl chloride and the amide was resolved chromatographically by using a 5 × 100 cm preparative column packed with CSP 1 on 40 μm irregular silica.[1,6] The initially eluted *R* enantiomer was hydrosilylated with triethoxysilane–chloroplatinic acid (neat 90 °C) and the chiral silane purified by rapid chromatography on silica. The purified silane was bonded to 5 μm Spherisorb silica (benzene, reflux 36 h) and the resultant material was slurry packed into a 4.6 × 250 mm column.

Figure 1 shows the resolution of methyl phenylalanate (as the 3,5-dinitrobenzamide) on CSP 2. Not only is the magnitude of α, the chromatographic separation factor, large (4.73) but band shapes are excellent and the resolution factor is unusually large (16.5) as a consequence. Table I provides chromatographic data for the resolution on this CSP of a variety of amines, amino alcohols, and amino acid esters and amides, all as the 3,5-dinitrobenzamide derivatives. In addition, the 3,5-dinitrobenzoates of several alcohols are included in Table I. In general, these solutes resolve quite readily, the magnitudes of α typically being appreciably greater than those reported[5] by Oi et al. for any given solute. Elution orders were established through chromatography of configurationally established partially resolved samples.

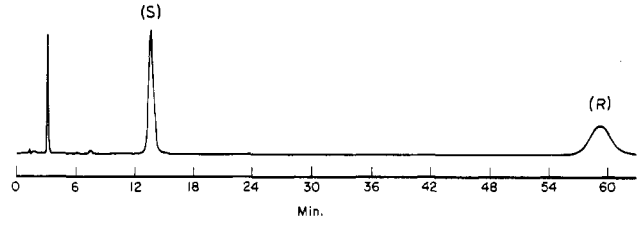

Figure 1. Chromatographic separation of methyl *N*-(3,5-dinitrobenzoyl)phenylalanate on CSP 2. The mobile phase was 20% isopropyl alcohol in *n*-hexane and the flow rate was 2 mL/min. A 254-nm ultraviolet absorption detector was used.

Also shown in Table I are data obtained on CSP 3, similarly derived from (*R*)-α-(1-naphthyl)ethylamine. This CSP was prepared after the appearance of Oi's paper to ascertain whether the high level of performance of CSP 2 actually stems from our choice of amine or from our

(4) Weinstein, S.; Feibush, B.; Gil-Av, E. *J. Chromatogr.* **1976**, *126*, 97
(5) Oi, N.; Nagase, M.; Doi, T. *J. Chromatogr.* **1983**, *257*, 111.
(6) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1982**, *47*, 4037.

Table II. Reverse-Phase Resolution of the *N*-3,5-Dinitrobenzoyl Derivatives of α-Amino Acids on CSP 2 and CSP 3

amino acids[e]	CSP 2			CSP 3		
	α[a]	k'_1[b]	conf[c]	α[a]	k'_1[b]	conf[c]
alanine	1.28	1.0	*S*	NR[d]		
valine	1.31	1.2	*S*	NR		
leucine	1.82	2.8	*S*	NR		
isoleucine	1.51	2.3	*S*	NR		
n-leucine	1.51	5.0	*S*	NR		
phenylglycine	1.90	3.3	*S*	1.36	8.0	*S*
4-OH-phenylglycine	1.77	2.6	*S*	1.45	3.5	*S*
methionine	1.27	3.8	*S*	NR		

[a] Chromatographic separability factor. [b] Capacity factor for the first eluted enantiomer using 20% methyl alcohol in water (0.2% $NaHCO_3$) as a mobile phase. [c] Absolute configuration of the second eluted enantiomer. [d] No resolution. [e] As DNB derivatives.

method of linking the amine to silica. Since CSP **3** also affords results generally superior to those reported by Oi et al., it appears that the longer and nonpolar linkage does indeed play a role in improving the performance of CSPs **2** and **3**.

Allowing for the difference in absolute configuration of the CSPs of Oi et al. and CSPs **2** and **3**, one notes that the relative elution order of solutes is, in the cases where comparison has been made, the same. However, the elution order we note for the amino acid derivatives in Table I typically is not the order we had expected. Experimentally, CSP (*R*)-**1** was found to selectively retain the *S* enantiomer of *N*-acylated α-(6,7-dimethyl-1-naphthyl)isobutylamines.[1] Hence CSP (*R*)-**2** was expected to selectively retain the *S* enantiomers of amides and (presumably) esters of the 3,5-dinitrobenzamide of phenylglycine and (presumably) other amino acids as well. While (*S*)-*N*-(3,5-dinitrobenzoyl)phenylglycine *n*-butylamide is selectively retained (albeit with a small α value) it is, among the amino acids yet studied, the only one that, while so derivatized, shows this elution order. Moreover, the *R* enantiomers of esters of *N*-3,5-dinitrobenzoyl amino acids, including phenylglycine, are the more strongly retained. This initially surprising result is, if fact, of great significance in terms of chiral recognition mechanisms.

In solution, chiral recognition is reciprocal.[7] However, the ability of bound enantiomer A to distinguish between the enantiomers of free B is not necessarily mirrored by the ability of bound enantiomer B to distinguish between the enantiomers of free A. In other words, the mode of attachment of a CSP to the support may influence the chiral recognition process. This aspect of CSP design is being studied and a more detailed discussion of the effects of attachment modes will be reported subsequently.

Table II provides chromatographic data for the reverse-phase resolution of α-amino acid 3,5-dinitrobenzamides on CSPs **2** and **3**. Two observations are easily made. First, CSP **2** is clearly superior to CSP **3** in terms of its scope and power. Secondly, the (reverse-phase) elution order of the acids is different than that noted for the direct-phase resolutions of the corresponding esters or amides. While a discussion of chiral recognition mechanisms is premature, it is clear that the ability to readily separate the enantiomers of *N*-3,5-dinitrobenzoyl amino acids provides a sensitive and facile method for determining enantiomeric purity and absolute configuration of α-amino acids. The *N*-3,5-dinitrobenzoyl group is easily introduced (3,5-dinitrobenzoyl chloride, propylene oxide, THF, 25 °C, ca. 15 min) without racemization and provides a strongly adsorbing chromophore to facilitate detection.

(7) Implicit in this statement is the assumption that chiral recognition stems from a 1:1 interaction between A and B and that neither A nor B self-associate to a significant degree. The statement becomes increasingly accurate as concentrations are reduced.

Experimental Section

Chromatography was performed by using a Beckman 100 A pump, Model 210 injector (20 μL loop), Model 165 detector, and a Kipp-Zonen BD 41 recorder. Ultraviolet adsorption of the eluent was monitored simultaneously at 254 and 280 nm.

Solutes. The solutes employed in this study were obtained from well-known compounds by acylation with 3,5-dinitrobenzoyl chloride. Usually, Schotten–Baumann conditions were employed. In the case of the amino acids, a modification of our earlier procedure[8] was used with superior results. An example of this procedure is provided.

(*S*)-*N*-(3,5-Dinitrobenzoyl)leucine. To a slurry of 13.1 g (0.1 mol) of (*S*)-leucine in 50 mL of dry THF was added 23.1 g (0.1 mol) of 3,5-dinitrobenzoyl chloride and 17.4 g (0.3 mol) of propylene oxide. The mixture warms slightly as the reaction proceeds. After 15 min, the solution was suction filtered to remove traces of residual leucine and evaporated to dryness in vacuo to afford (*S*)-*N*-(3,5-dinitrobenzoyl)leucine (32.9 g) of high purity (>98% enantiomeric purity by HPLC assay) and in essentially quantitative yield. If desired, this material may be recrystallized from acetonitrile. Physical properties agree with those previously reported.[8]

(*R*)-*N*-(11-(Triethoxysilyl)undecanoyl)-α-(6,7-dimethyl-1-naphthyl)isobutylamine. To a 50-mL round-bottom flask equipped with a reflux condensor, nitrogen atmosphere, and magnetic stirrer was added 1.97 g (0.005 mol) of enantiomerically pure (*R*)-*N*-(10-undecenoyl)-α-(6,7-dimethyl-1-naphthyl)isobutylamine[1] and 10 mL of triethoxysilane. The mixture was warmed to 40 °C and 0.8 mL of a chloroplatinic acid solution (71.5 mg in 20 mL of isopropyl alcohol) was added. The mixture was warmed to 90 °C and stirred at this temperature for 1 h. The excess triethoxysilane was removed in vacuo and the residue was chromatographed rapidly upon silica (10:1 CH_2CH_2–ethyl acetate) to afford the hydrosilylated product (1.48 g) as a white solid: mp 52–54 °C in 53% yield; ^1H NMR ($CDCl_3$) δ 0.60 (t, 2 H), 0.87 (d, 3 H), 1.03 (d, 3 H), 1.10–1.77 (m, 25 H), 2.00–2.30 (m, 3 H), 2.37 (s, 3 H), 2.42 (s, 3 H), 3.77 (q, 6 H), 5.47–5.83 (m, 2 H), 7.23 (d, 2 H), 7.47–7.63 (m, 2 H), 7.87 (s, 1 H); IR (KBr) cm^{-1} 3300, 2970, 2925, 2854, 1630, 1530; high-resolution mass spectrum, calcd for $C_{33}H_{55}NO_4Si$ 557.3900, found 557.3905, $[\alpha]^{25}_D$ −28.5 (*c* 0.58, CH_2Cl_2).

A major side reaction is reduction of the alkene.

(*R*)-*N*-(11-(Triethoxysilyl)undecanoyl)-α-(1-naphthyl)-ethylamine. This chiral silane was made in a manner analogeous to that described above and isolated as a colorless oil in 63% yield: ^1H NMR ($CDCl_3$) δ 0.60 (t, 2 H), 1.13–1.75 (m, 25 H), 1.67 (d, 3 H), 2.07–2.27 (m, 2 H), 3.82 (q, 6 H), 5.57–5.77 (m, 1 H), 5.80–6.03 (m, 1 H), 7.40–8.17 (m, 7 H); IR (KBr) cm^{-1} 3285, 3050, 2975, 2925, 2855, 1638, 1545; high-resolution mass spectrum, calcd for $C_{29}H_{47}NO_4Si$ 501.3274, found 501.3260; $[\alpha]^{25}_D$ +27.5 (*c* 1.09, CH_2Cl_2).

Chiral Stationary Phases 2 and 3. Water was azeotropically removed (Dean–Stark trap) from a slurry of 4.5 g of 5 μm Spherisorb in 50 mL of benzene in a 250-mL round-bottom flask fitted with a mechanical stirrer. After drying was complete, 5 mmol of the appropriate hydrosilyated amide was added and the

(8) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1981**, *46*, 2935.

gently stirred slurry was maintained at reflux for 36 h under a nitrogen atmosphere. The modified silica was collected by filtration and washed thoroughly with benzene, ethyl acetate, methanol, acetone, ether, and pentane. After vacuum drying, elemental analysis of the CSPs afforded the following.

CSP 2 Anal. Found: C, 7.33; H, 1.00; N, 0.24; Si, 42.62. Calcd: 0.17 mmol of amide/g (based on N); 0.21 mmol of amide/g (based on C).

CSP 3 Anal. Found: C, 8.27; H, 1.07; N, 0.42; Si, 42.08. Calcd: 0.30 mmol/g (based on N); 0.28 mmol/g (based on C).

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Registry No. (±)-I (X = NH, R_1 = CH_3, R_2 = $COOCH_3$), 74928-18-0; (±)-I (X = NH, R_1 = i-C_3H_7, R_2 = $COOCH_3$), 74928-20-4; (±)-I (X = NH, R_1 = i-C_4H_9, R_2 = $COOCH_3$), 74928-21-5; (±)-I (X = NH, R_1 = t-C_7H_9, R_2 = $COOCH_3$), 90696-95-0; (±)-I (X = NH, R_1 = phenyl, R_2 = $COOCH_3$), 74928-23-7; (±)-I (X = NH, R_1 = benzyl, R_2 = $COOCH_3$), 74928-24-8; (±)-I (X = NH, R_1 = 4-F-benzyl, R_2 = $COOCH_3$), 90696-96-1; (±)-I (X = NH, R_1 = α-naphthyl, R_2 = $COOCH_3$), 90696-97-2; (±)-I (X = NH, R_1 = CH_3, R_2 = CONH-n-Bu), 74928-25-9; (±)-I (X = NH, R_1 = i-C_3H_7, R_2 = CONH-n-Bu), 74928-26-0; (±)-I (X = NH, R_1 = i-C_4H_9, R_2 = CONH-n-Bu), 74928-27-1; (±)-I (X = NH, R_1 = phenyl, R_2 = CONH-n-Bu), 74928-29-3; (±)-I (X = NH, R_1 = benzyl, R_2 = CONH-n-Bu), 74928-30-6; (±)-I (X = NH, R_1 = C_2H_5, R_2 = CH_2OH), 90696-98-3; (±)-I (X = NH, R_1 = C_2H_5, R_2 = CH_2OMe), 90696-99-4; (±)-I (X = NH, R_1 = i-C_3H_7, R_2 = CH_2OH), 74928-36-2; (±)-I (X = NH, R_1 = phenyl, R_2 = CH_3), 14402-00-7; (±)-I (X = NH, R_1 = phenyl, R_2 = i-C_3H_7), 74927-94-9; (±)-I (X = NH, R_1 = benzyl, R_2 = CH_3), 14402-01-8; (±)-I (X = NH, R_1 = n-C_4H_9, R_2 = CH_3), 90697-00-0; (±)-I (X = NH, R_1 = n-C_5H_{11}, R_2 = CH_3), 90697-01-1; (±)-I (X = O, R_1 = phenyl, R_2 = CH_3), 21286-22-6; (±)-I (X = O, R_1 = phenyl, R_2 = t-C_4H_9), 74928-02-2; (±)-I (X = O, R_1 = phenyl, R_2 = n-C_4H_9), 90697-02-2; (±)-I (X = O, R_1 = phenyl, R_2 = cyclopropyl), 74928-01-1; (±)-I (X = O, R_1 = 4-Cl-phenyl, R_2 = CH_3), 74928-07-7; (±)-I (X = O, R_1 = 9-anthryl, R_2 = CH_3), 74928-10-2; (R)-I (X = NH, R_1 = CH_3, R_2 = $COOCH_3$), 69632-41-3; (R)-I (X = NH, R_1 = i-C_3H_7, R_2 = $COOCH_3$), 69632-45-7; (R)-I (X = NH, R_1 = i-C_4H_9, R_2 = $COOCH_3$), 90697-03-3; (R)-I (X = NH, R_1 = t-C_4H_9, R_2 = $COOCH_3$), 90761-56-1; (R)-I (X = NH, R_1 = phenyl, R_2 = $COOCH_3$), 69632-50-4; (R)-I (X = NH, R_1 = benzyl, R_2 = $COOCH_3$), 69632-43-5; (R)-I (X = NH, R_1 = CH_3, R_2 = CONH-n-Bu), 69632-52-6; (R)-I (X = NH, R_1 = i-C_3H_7, R_2 = CONH-n-Bu), 69632-54-8; (R)-I (X = NH, R_1 = i-C_4H_9, R_2 = CONH-n-Bu), 90761-57-2; (S)-I (X = NH, R_1 = phenyl, R_2 = CONH-n-Bu), 69632-59-3; (R)-I (X = NH, R_1 = benzyl, R_2 = CONH-n-Bu), 69632-56-0; (R)-I (X = NH, R_1 = C_2H_5, R_2 = CH_2OH), 90761-58-3; (R)-I (X = NH, R_1 = C_2H_5, R_2 = CH_2OCH_3), 90761-59-4; (R)-I (X = NH, R_1 = i-C_3H_7, R_2 = CH_2OH), 90761-60-7; (R)-I (X = NH, R_1 = phenyl, R_2 = CH_3), 69632-32-2; (R)-I (X = NH, R_1 = phenyl, R_2 = i-C_3H_7), 69632-36-6; (S)-I (X = NH, R_1 = benzyl, R_2 = CH_3), 15719-22-9; (R)-I (X = NH, R_1 = benzyl, R_2 = CH_3), 86118-08-3; (S)-N-(3,5-dinitrobenzoyl)leucine, 7495-01-4; (S)-leucine, 61-90-5; 3,5-dinitrobenzoyl chloride, 99-33-2; (R)-N-(11-(triethoxysilyl)-undecanoyl)-α-(6,7-dimethyl-1-naphthyl)isobutylamine, 90697-04-4; (R)-N-(10-undecenoyl)-α-(6,7-dimethyl-1-naphthyl)isobutylamine, 90761-61-8; triethoxysilane, 998-30-1; (R)-N-(11-(triethoxysilyl)undecanoyl)-α-(1-naphthyl)ethylamine, 90718-44-8; N-(3,5-dinitrobenzoyl)-DL-alanine, 74928-52-2; N-(3,5-dinitrobenzoyl)-DL-valine, 74928-53-3; N-(3,5-dinitrobenzoyl)-DL-leucine, 74928-54-4; N-(3,5-dinitrobenzoyl)-DL-isoleucine, 74928-60-2; N-(3,5-dinitrobenzoyl)-DL-n-leucine, 90697-05-5; N-(3,5-dinitrobenzoyl)-DL-phenylglycine, 74958-71-7; N-(3,5-dinitrobenzoyl)-DL-4-OH-phenylglycine, 90697-06-6; N-(3,5-dinitrobenzoyl)-DL-methionine, 74928-56-6; N-(3,5-dinitrobenzoyl)-(S)-alanine, 58248-10-5; N-(3,5-dinitrobenzoyl)-(S)-valine, 77495-25-1; N-(3,5-dinitrobenzoyl)-(S)-isoleucine, 90697-07-7; N-(3,5-dinitrobenzoyl)-(S)-n-leucine, 90697-08-8; N-(3,5-dinitrobenzoyl)-(S)-phenylglycine, 90761-62-9; N-(3,5-dinitrobenzoyl)-(S)-4-OH-phenylglycine, 90761-63-0; N-(3,5-dinitrobenzoyl)-(S)-methionine, 58248-12-7.

Oxidation of Phenols with Iodine in Alkaline Methanol

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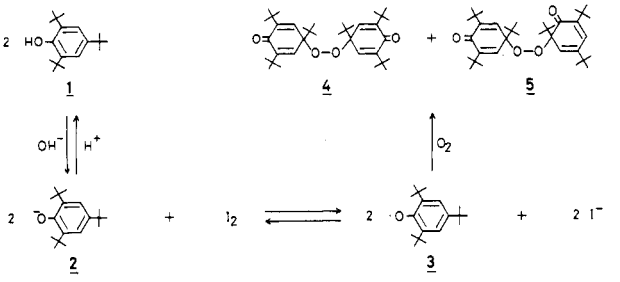
The use of iodine as an oxidizing agent for phenolic compounds has been explored. The reaction has been conducted in methanol containing such alkali as potassium hydroxide and, depending on the nature of the substituents and on the amount of iodine employed, leads to iodination, oxidation to give a stable phenoxy radical, oxidative dimerization, or benzylic oxidation. In general the reaction proceeds smoothly at room temperature, and under appropriate conditions yields of products are good to excellent. Oxidative dimerization of 2,4- and 2,6-di-*tert*-butylphenols involves iodination followed by iodine-catalyzed dimerization. The oxidation of 4-methylphenols with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in methanol has been carried out for comparison.

Iodine under basic condition is a known reagent for iodination of phenols. The reagent has occasionally been reported to bring about oxidative coupling of certain phenolic substances under appropriate conditions,[1,2] but a systematic study on the use of iodine as an oxidizing agent for phenols has not appeared. I have investigated the oxidation of phenols with iodine in alkaline methanol, and this paper reports the results.

Results and Discussion

2,4,6-Tri-*tert*-butylphenol (1). Addition of a methanolic iodine (0.5 molar equiv) solution to a solution of 1 in methanol containing excess potassium hydroxide (KOH) immediately afforded blue 2,4,6-tri-*tert*-butylphenoxy radical **3**. Introduction of oxygen into the blue solution gave quinolide peroxides **4** (47%) and **5** (41%) as the al-

Scheme I



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