Workup of Hydrogenation Product. The corresponding solutions of 2-acetamido- or -benzamido-3-hetarylpropanoic acids after hydrogenation were evaporated to dryness, and one of the following procedures was used to isolate the hydrogenation product.

A. In the cases of 2-acetamido-3-(3-pyridyl)propanoic acid (**7a**) and 2-acetamido-3-(3-quinolyl)propanoic acid (**6a**) the residue was dissolved in water and separated from the insoluble catalyst by filtration. Evaporation to dryness afforded the product; yields were essentially 100% except for the slowest reactions (time ≳1440 min).

B. In the cases of 2-benzamido-3-(2-thienyl)propanoic acid (**1b**), 2-benzamido-3-(2-furyl)propanoic acid (**3b**), 2-benzamido-3-[1-methylpyrrol-2-yl]propanoic acid (**4b**), 2-benzamido-3-(3-indolyl)propanoic acid (**5b**), 2-benzamido-3-(3-pyridyl)propanoic acid (**7b**), 2-benzamido-3-(3-quinolyl)propanoic acid (**6b**), and 2-benzamido-3-(3-thienyl)propanoic acid (**2b**), the residue was dissolved in 0.5 N sodium hydroxide and separated from the insoluble catalyst by filtration. The filtrate was acidified with dilute hydrochloric acid and the precipitate filtered and dried, giving the desired product.

C. In the cases of 2-acetamido-3-(2-thienyl)propanoic acid (**1a**), 2-acetamido-3-(2-furyl)propanoic acid (**3a**), and 2-acetamido-3-(3-indolyl)propanoic acid (**5a**), the residue was dissolved in 0.5 N sodium hydroxide and separated from the insoluble catalyst by filtration. The filtrate was acidified with dilute hydrochloric acid and extracted with diethyl ether. The ethereal extract was dried and evaporated to dryness to afford the product.

Acknowledgment. This research was made possible by the generous financial support of the Comisiõn Asesora de Investigaciõn Científica y Tēcnica. We are grateful to Prof. Ernest L. Eliel for his criticism and helpful suggestions for the preparation of this manuscript. We are indebted to Mme. M. F. Grenier (University of Pau, France) for her help and advice with regard to the NMR measurements.

Registry No. **1a**, 83396-73-0; **1b**, 83396-72-9; **2b**, 88991-22-4; **3a**, 89908-19-0; **3b**, 89890-88-0; **4b**, 89890-89-1; **5a**, 70082-70-1; **5b**, 85622-38-4; **6a**, 89890-90-4; **6b**, 89890-91-5; **7a**, 89890-92-6; **7b**, 89890-93-7; $[RhCl(COD)]_2$, 12092-47-6; (-)-DIOP, 32305-98-9; $[Rh(COD)$-(-)-$DIOP]ClO_4$, 70832-57-4; (*R*)-2-acetamido-3-(2-thienyl)propanoic acid, 83396-77-4; (*R*)-2-benzamido-3-(2-thienyl)propanoic acid, 83396-74-1; (*R*)-2-benzamido-3-(3-thienyl)propanoic acid, 89921-39-1; (*R*)-2-acetamido-3-(2-furyl)propanoic acid, 89890-94-8; (*R*)-2-benzamido-3-(2-furyl)propanoic acid, 89955-20-4; (*R*)-2-benzamido-3-[2-(1-methyl)pyrrolyl]propanoic acid, 89890-95-9; (*R*)-2-acetamido-3-(3-indolyl)propanoic acid, 2280-01-5; (*R*)-2-benzamido-3-(3-indolyl)propanoic acid, 55629-71-5; (*R*)-2-acetamido-3-(3-quinolyl)propanoic acid, 89890-96-0; (*R*)-2-benzamido-3-(3-quinolyl)propanoic acid, 89890-97-1; (*R*)-2-acetamido-3-(3-pyridyl)propanoic acid, 89890-98-2; (*R*)-2-benzamido-3-(3-pyridyl)propanoic acid, 89955-25-9.

Chromatographic Separation of the Enantiomers of N-Acylated Heterocyclic Amines

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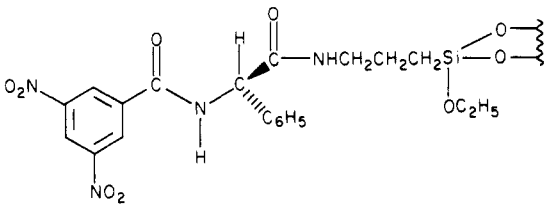
Received September 13, 1983

In a previous paper, we have described the use of chiral stationary phase (CSP) 1 for the liquid chromatographic separation of enantiomers of assorted amines, amino alcohols, esters, and C-terminal amides of α-amino acids, all as the N-α-naphthoyl derivatives. Herein, we extend this method to cover a number of heterocyclic amines.

The column used in this study is a commercial version[1] of our previously reported[2] covalently bound (R)-*N*-(3,5-dinitrobenzoyl)phenylglycine stationary phase, 1.[3] Table



1

I gives data pertinent to the elution order and chromatographic separability of the enantiomers of a variety of N-α-naphthoyl heterocyclic amines, some of which are themselves or are closely related to compounds that are of pharmacological interest. Accordingly, this technique should be of considerable utility to chemists and pharmacologists as a means of both determining enantiomeric purity and absolute configuration on microgram quantities of material and preparatively resolving large quantities of material.[5]

The order of elution of the enantiomers from a given chiral column is determined by their stereochemistry. The absolute configuration of a given amine may be determined by chromatographic comparison with authentic, configurationally known material, collection of one enantiomer for chiroptic evaluation, or from chiral recognition models that relate stereochemistry to elution order. While the absolute configurations of relatively few of the compounds in the table have thus far been rigorously related to elution order, it is believed that, for all of the compounds of type **2**, **3**, and **5** shown in the table, the most strongly retained enantiomer has the configuration indicated. Note that the elution order of enantiomers from this type of column, coupled with asymmetric synthesis data, has already been used in the assignment of absolute configuration of several of the tetrahydroisoquinolines listed in the table.[6]

Although we have postulated chiral recognition models to account for the separation of other enantiomeric amides on CSP 1, we defer detailed discussion of the mechanism(s) presently operative. Such discussion would require knowledge of the conformational preferences of both CSP and solutes. Arguments relevant to the former have been presented, but conformational behavior of the latter is still unknown. In the case of the naphthamide solutes, the amide nitrogen and its adjoining carbons would prefer, for electronic reasons, to be coplanar with the α-naphthoyl system. However, steric interaction with the proximate peri and β-hydrogens of the naphthyl system undoubtedly cause some departure from coplanarity. The sense and

(1) Regis Chemical Co., 8010 Austin Ave., Morton Grove, IL 60053. J. T. Baker Chemical Co. also offers a covalent column of this type that is satisfactory in this application.

(2) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, *192*, 143.

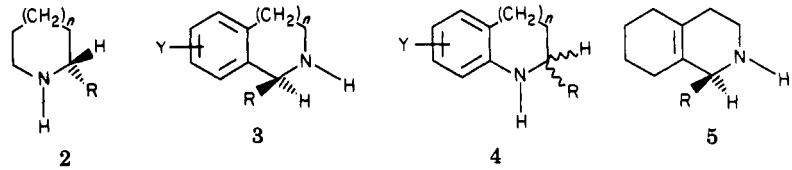
(3) The reported separations can also be effected with use of commercial columns (Regis, J. T. Baker, Chemical Co.) packed with the ionically bound version[4] of CSP 1.

(4) (a) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1981**, *46*, 2935. (b) Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 3964.

(5) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1982**, *47*, 4037.

(6) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117.

Table I



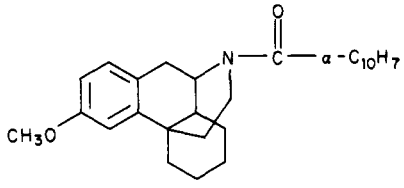
2 3 4 5

compd type	Y	R	n	α^a	$\kappa_1'^b$	% IPA[c]	retained enantiomer
2		CH_3	0	1.11	8.6	10	S-(+)[d]
2		n-C_4H_9	0	1.13	18.5	5	
2		CH_3	1	1.15	4.7	10	S-(+)[d]
2		C_2H_5	1	1.19	4.0	10	(+)[d]
2		n-C_3H_9	1	1.25	11.7	5	(+)[d]
2		n-C_4H_9	1	1.13	18.3	5	
2		n-C_5H_{11}	1	1.25	10.0	5	(+)[d]
2		C_6H_5	1	1.19	7.6	10	(+)[d]
2		$CH_2CH(c\text{-}C_6H_{11})_2$	1	1.23	7.6	10	(+)[d]
3		CH_3	1	1.33	10.9	10	(−),[d] S-(−)
3		n-C_4H_9	1	1.50	7.5	10	S-(−)
3		i-C_4H_9	1	1.53	8.7	10	(+),[d] S-(−)
3		Bz	1	1.42	7.5	10	S-(−)
3		$C_6H_5(CH_2)_2$	1	1.45	10.3	10	S-(+)
3	4,5-$(OCH_3)_2$	CH_3	1	1.24	42	10	
4		CH_3	0	1.03	~8	1	
4		C_2H_5	0	1.06	~11	1	
4		CH_3	1	1.31	4.9	10	(−),[d] R-(+)
5		p-$CH_3OC_6H_4CH_2$		1.39	9.6	10	S-(−), (−)[d]

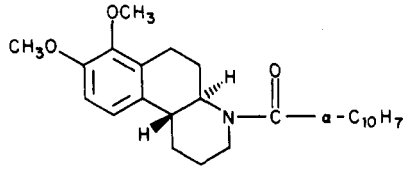
[a] The magnitude of α, the chromatographic separability factor is κ_2'/κ_1', where κ_1' and κ_2' are the capacity ratios of the enantiomers. [b] $\kappa^{1\prime}$ is the capacity ratio for the first enantiomer eluted. [c] Percent isopropyl alcohol (in hexane) used as mobile phase. [d] Rotational sign of the most strongly retained amide enantiomer. Unmarked signs refer to the rotation of the amine enantiomer from which thee amide was derived. Rotations of the amides were determined with a Rudolph Autopol III as a secondary HPLC detector. All rotational signs are those noted at 589 nm.

extent of this "twist" might have some bearing upon chiral recognition. Moreover, the position of the equilibrium between E and Z rotamers of the heterocyclic amides is expected to be important in the chiral recognition process.

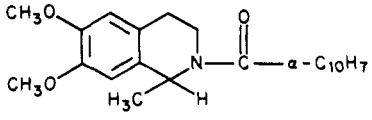
Several more complex heterocycles have, as the α-naphthamides, been resolved and are listed individually (**6**–**9**).



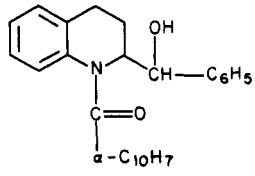
6, α = 1.24



7, α = 1.05



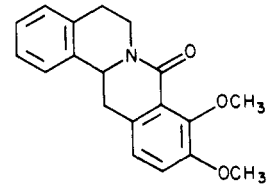
8, α = 1.21



9, α = 1.85 minor[9] diastereomer
α = 1.10 major[9] diastereomer

Heterocyclic amines in which the chiral center is remote from nitrogen have not been extensively studied. It is to be noted, however, that under conditions that allow separation of the enantiomers of *N*-α-naphthoyl-α-picoline (α = 1.11), the corresponding enantiomers derived from β-picoline are inseparable (α = 1.00).

Finally, we point out that although α-naphthamide derivatives have been found useful in this application, other acylating agents may be found to suffice in some instances. Note that lactam **10** requires no derivatization prior to resolution.



10, α = 1.11

Experimental Section

General Data. Chromatography was performed with a Beckman A-100 pump, 210 injector, and Model 165 variable-wavelength detector. A. Rudolph Autopol III with a 20-cm flow cell was used to monitor $[\alpha]_D$. The column employed was a Regis Covalent Pirkle-1A.

Solutes. The solutes used in this study were prepared by treating a methylene chloride solution of the amine with a slight excess of α-naphthoyl chloride.[10] The solution was washed se-

(7) Pirkle, W. H.; Welch, C. J.; Hyun, M. H. *J. Org. Chem.* **1983**, *48*, 5022.
(8) Pirkle, W. H.; Welch, C. J. *J. Org. Chem.* **1984**, *49*, 138.
(9) Meyers, A. I.; Hellring, S. *Tetrahedron Lett.* **1981**, *22*, 5119.
(10) The commercial α-naphthoic acid used in this study was found to contain some of the β-isomer. Unless removed, this contaminant produces a second, usually forerunning, pair of peaks for the enantiomers. Recrystallization from toluene is a satisfactory method of purification.

quentially with 2 M sodium hydroxide, 2 M hydrochloric acid, and water, then dried, and filtered prior to injection. In several instances, the α-naphthamides of amines used in this study were isolated and shown to have properties corresponding to reported literature values. Most of the amines used in this study are well-known and were from commercial sources or from prior studies. Asymmetric syntheses of some of the amines employed have been reported by Meyers and Fuentes.[6]

Acknowledgment. This work has been supported in part by the National Science Foundation. We are grateful to Hoffman-La Roche, Inc. and Merrell Dow Pharmaceuticals, Inc. for several of the amines used in this study.

Registry No. 1, 74927-72-3; (±)-2 (R = Me; n = 0), 79171-53-2; (*R*)-2 (R = Me; n = 0) *N*-α-naphthoyl derivative, 90132-84-6; (*S*)-2 (R = Me; n = 0) *N*-α-naphthoyl derivative, 90132-85-7; (±)-2 (R = Bu; n = 0), 90132-74-4; (*R*)-2 (R = Bu; n = 0) *N*-α-naphthoyl derivative, 90132-86-8; (*S*)-2 (R = Bu; n = 0) *N*-α-naphthoyl derivative, 90132-87-9; (±)-2 (R = Me; n = 1), 3000-79-1; (*R*)-2 (R = Me; n = 1) *N*-α-naphthoyl derivative, 90132-88-0; (*S*)-2 (R = Me; n = 1) *N*-α-naphthoyl derivative, 90132-89-1; (±)-2 (R = Et; n = 1), 78738-37-1; (*R*)-2 (R = Et; n = 1) *N*-α-naphthoyl derivative, 90132-90-4; (*S*)-2 (R = Et; n = 1) *N*-α-naphthoy derivative, 90132-91-5; (±)-2 (R = Pr; n = 1), 3238-60-6; (*R*)-2 (R = Pr; n = 1) *N*-α-naphthoyl derivative, 90132-92-6; (*S*)-2 (R = Pr; n = 1) *N*-α-naphthoyl derivative, 90132-93-7; (±)-2 (R = Bu; n = 1), 68144-45-6; (*R*)-2 (R = Bu; n = 1) *N*-α-naphthoyl derivative, 90132-94-8; (*S*)-2 (R = Bu; n = 1) *N*-α-naphthoyl derivative, 90132-95-9; (±)-2 (R = $(CH_2)_4CH_3$; n = 1), 90132-75-5; (*R*)-2 (R = $(CH_2)_4CH_3$; n = 1) *N*-α-naphthoyl derivative, 90132-96-0; (*S*)-2 (R = $(CH_2)_4CH_3$; n = 1) *N*-α-naphthoyl derivative, 90132-97-1; (±)-2 (R = Ph; n = 1), 90192-86-2; (*R*)-2 (R = Ph; n = 1) *N*-α-naphthoyl derivative, 90132-98-2; (*S*)-2 (R = Ph; n = 1) *N*-α-naphthoyl derivative, 90132-99-3; (±)-2 (R = $CH_2CH(c\text{-}C_6H_{11})_2$; n = 1), 35193-73-8; (*R*)-2 (R = $CH_2CH(c\text{-}C_6H_{11})_2$; n = 1) *N*-α-naphthoyl derivative, 90133-00-9; (*S*)-2 (R = $CH_2CH(c\text{-}C_6H_{11})_2$; n = 1) *N*-α-naphthoyl derivative, 90133-01-0; (±)-3 (R = Me; Y = H; n = 1), 90192-87-3; (*R*)-3 (R = Me; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-02-1; (*S*)-3 (R = Me; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-03-2; (±)-3 (R = Bu; Y = H; n = 1), 90192-88-4; (*R*)-3 (R = Bu; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-04-3; (*S*)-3 (R = Bu; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-05-4; (±)-3 (R = *i*-Bu; Y = H; n = 1), 90192-89-5; (*R*)-3 (R = *i*-Bu; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-06-5; (*S*)-3 (R = *i*-Bu; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-07-6; (±)-3 (R = Bz; Y = H; n = 1), 90132-76-6; (*R*)-3 (R = Bz; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-08-7; (*S*)-3 (R = Bz; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-09-8; (±)-3 (R = $Ph(CH_2)_2$; Y = H; n = 1), 90192-90-8; (*R*)-3 (R = $Ph(CH_2)_2$; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-10-1; (*S*)-3 (R = $Ph(CH_2)_2$; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-11-2; (±)-3 (R = Me; Y = 4,5-$(OMe)_2$; n = 1), 38520-68-2; (*R*)-3 (R = Me; Y = 4,5-$(OMe)_2$; n = 1) *N*-α-naphthoyl derivative, 90192-91-9; (±)-3 (R = Me; Y = H; n = 0), 90132-77-7; (*R*)-3 (R = Me; Y = H; n = 0) *N*-α-naphthoyl derivative, 90133-12-3; (*S*)-3 (R = Me; Y = H; n = 0) *N*-α-naphthoyl derivative, 90133-13-4; (±)-3 (R = Et; Y = H; n = 0), 90132-78-8; (*R*)-3 (R = Et; Y = H; n = 0) *N*-α-naphthoyl derivative, 90133-14-5; (*S*)-3 (R = Et; Y = H; n = 0) *N*-α-naphthoyl derivative, 90133-15-6; (±)-4 (R = Me; Y = H; n = 1), 74497-74-8; (*R*)-4 (R = Me; Y = H; n = 1) *N*-α-naphthoyl derivative, 90133-16-7; (*S*)-4 (R = Me; Y = H; n = 1) *N*-α-naphthyl derivative, 90133-17-8; (±)-5 (R = *p*-$CH_3OC_6H_4CH_2$), 57849-23-7; (*R*)-5 (R = *p*-$CH_3OC_6H_4CH_2$) *N*-α-naphthoyl derivative, 90133-18-9; (*S*)-5 (R = *p*-$CH_3OC_6H_4CH_2$) *N*-α-naphthoyl derivative, 90133-19-0; (±)-6, 90147-60-7; (±)-7, 90132-79-9; (±)-8, 90132-80-2; (±)-9 (isomer 1), 90132-81-3; (±)-9 (isomer 2), 90132-82-4; (±)-10, 90132-83-5; (*S*)-3 (R = Me; Y = 4,5-$(OMe)_2$; n = 1) *N*-α-naphthoyl derivative, 90192-92-0.

Metabolites of the Pulmonate *Siphonaria lessoni*

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Received December 28, 1983

The pulmonates are air-breathing gastropod molluscs found in the high intertidal region. Previous studies of pulmonates of the genus *Siphonaria* have reported the isolation of antimicrobial metabolites having "polypropionate" carbon skeletons. The major metabolites of *S. diemenensis* from southeastern Australia are diemenensin-A (**1**) and diemenensin-B (**2**).[1] *Siphonaria pectinata* from Florida contained pectinatone (**3**).[2] We now report the isolation and characterization of norpectinatone (**4**) and *E* and *Z* isomers of a related furanone, **5** and **6**, from the Chilean pulmonate *Siphonaria lessoni* (Chart I).

The pulmonate *Siphonaria lessoni* was collected intertidally at Dichato, Cocholgue, and the Bio-Bio River mouth, all near Concepcion, Chile. Each collection was stored separately in acetone. The acetone extracts of the three samples were identical by chromatographic and ^1H NMR analyses. The combined extracts were fractionated by medium-pressure silica chromatography, and the "polypropionate" fraction was further purified by precipitation of the sterols from acetonitrile. The acetonitrile-soluble material was separated by LC on Partisil by using ether as eluant to obtain two "polypropionate" fractions that comprised norpectinatone (**4**) and a 1:1 mixture of *E* and *Z* furanones **5** and **6**. The geometrical isomers could not be separated by HPLC.

Norpectinatone (**4**), $[\alpha]_D$ +49.2° (*c* 2.5, $CHCl_3$), was isolated as an oil. The similarity between norpectinatone (**4**) and pectinatone (**3**) was obvious from the spectral data. The high-resolution mass measurement (m/z 320.2367) defined the molecular formula as $C_{20}H_{32}O_3$. A major fragment ion at m/z 207 was caused by allylic cleavage resulting in the loss of a C_8H_{17} fragment. The ultraviolet spectrum [300 nm (ε 7600), 232 nm (ε 13 100)] was similar to that reported for pectinatone (**3**) [301 nm (ε 5063)].[2] The ^{13}C NMR spectrum contained signals at δ 165.9 (s), 165.5 (s), 159.2 (s), 106.5 (s), and 98.7 (s) for the pyrone carbons and at δ 126.1 (s) and 142.8 (d) for the olefinic carbons. These data indicated the presence of a 5-(2-alkyl-1-methylvinyl)pyrone, similar in structure to pectinatone (**3**) but lacking one methylene group in the alkyl chain. The ^1H NMR spectrum contained one terminal methyl signal at δ 0.81 (t, 3 H, J = 7 Hz) and three secondary methyl signals at δ 0.86 (d, 6 H, J = 6 Hz) and 0.99 (d, 3 H, J = 6.5 Hz) with the latter signal coupled to an allylic proton signal at δ 2.65 (m). The major differences between the ^{13}C NMR spectra of the pectinatone (**3**) and norpectinatone (**4**) can be ascribed to the replacement of a terminal propyl group [δ 14.3 (q), 19.9 (t), and 39.2 (t)] by an ethyl group [δ 11.2 (q) and 29.3 (t)].[3]

Ozonolysis of norpectinatone (**4**) followed by oxidation of the ozonide gave 2,4,6-trimethyloctanoic acid, $[\alpha]_D$ +39° that was transformed into methyl 2,4,6-trimethyloctanoate, $[\alpha]_D$ +46°, by using ethereal diazomethane solution. We have *tentatively* assigned the absolute stereochemistry as 2*S*,4*R*,6*S*, similar to that of pectinatone (**3**), on the fol-

(1) Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1983**, *24*, 1917.
(2) Biskupiak, J. E.; Ireland, C. *Tetrahedron Lett.* **1983**, *24*, 3055.
(3) Calculated ^{13}C NMR shifts for the terminal ethyl group are δ 10.9 and 29.8 (Lindeman–Adams Rules).

0022-3263/84/1949-2506$01.50/0