2 H), 3.8–4.55 (m, 3 H); mass spectrum, m/e $M^{+\cdot}$ absent, 215, 159 (base). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.85; H, 8.74.

[1*R*(*S*)]-5[*R*(*S*)]-Methoxy-7[*S*(*R*)]-methyl-2,6-dioxabicyclo[3.3.0]octan-3-one (37). CF_3CO_2H (0.5 mL) was added to **36** (0.25 g) in MeOH (9.5 mL) at 0 °C under nitrogen. After 1 h, evaporation and chromatography (petroleum ether–CH_2Cl_2 gradient 4:1–0:1) gave **37** (0.10 g, 54%) as a colorless oil: IR 1790 cm^{-1}; NMR (250 MHz) δ 1.34 (d, 3 H, J = 6.0 Hz), 1.74 (ddd, 1 H, J = 13.7, 8.2, 2.3 Hz), 2.55 (overlapping ddd as 5 lines, 1 H), 2.85 (AB q, 2 H, J = 16.4 Hz), 3.34 (s, 3 H), 4.32 (m, 1 H), 4.76 (dd, 1 H, J = 7.0, 2.3 Hz); mass spectrum, m/e 172 ($M^{+\cdot}$) 157, 141, 101 (base). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.58; H, 7.27.

Acknowledgment. We thank the Science and Engineering Research Council for a studentship and for the provision of a Bruker WM 250-MHz NMR spectrometer, W. R. Grace and Co., Research Division, for most generous support, and Professor I. O. Sutherland for spectra of nonactic acid derivatives.

Registry No. (±)-**1a**, 87598-04-7; **13b**, 87598-05-8; (±)-**14b**, 87598-06-9; (±)-**15a**, 87598-07-0; (±)-**15b**, 87598-08-1; (±)-**15c**, 87598-09-2; (±)-**16a**, 82242-81-7; (±)-**16b**, 87598-10-5; **17**, 41162-32-7; 18, 82242-80-6; (±)-**21a**, 13942-72-8; (±)-**21b**, 87598-11-6; (±)-**21c**, 87598-13-8; (±)-**21d**, 87598-12-7; (±)-**21e**, 87598-14-9; (±)-**22a**, 87678-04-4; (±)-**22b**, 87598-15-0; (±)-**23a**, 87678-05-5; (±)-**23b**, 87598-16-1; **27a**, 87678-06-6; **27b**, 87598-17-2; **28**, 1099-45-2; (±)-**30a**, 82242-83-9; (±)-**30b**, 82242-84-0; (±)-**31**, 82242-85-1; (±)-**32**, 82242-86-2; (±)-**33**, 82264-56-0; (±)-34, 58703-67-6; (±)-**35**, 87678-07-7; (±)-**36** (isomer), 87598-19-4; (±)-**36** (isomer 2), 87598-18-3; (±)-**37**, 87598-20-7; CH_3CHO, 75-07-0; di-*tert*-butyl oxalate, 691-64-5; *tert*-butyl acetate, 540-88-5; *tert*-butyl 3-oxobutanoate, 1694-31-1; *tert*-butyl (±)-2-methyl-3-oxobutanoate, 87598-21-8; *tert*-butyl propanoate, 20487-40-5.

A Chiral Recognition Model for the Chromatographic Resolution of N-Acylated 1-Aryl-1-aminoalkanes

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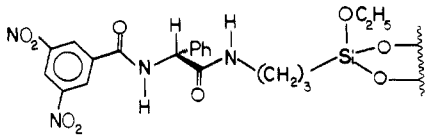
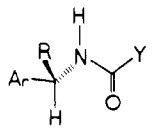
The enantiomers of *N*-acyl derivatives of 1-aryl-1-aminoalkanes generally may be chromatographically separated on a silica-bonded chiral stationary phase derived from *N*-(3,5-dinitrobenzoyl)phenylglycine. Chiral recognition is enhanced by increases in either the π basicity of the aryl substituent or the size of the alkyl substituent but is diminished by increases in the size of the acyl group. Carbamate and urea derivatives of these amines are also resolvable. Chiral recognition models are proposed to account for the observed chiral recognition and are used to assign absolute configuration to several acylated amines.

The enantiomers of a number of chiral amines can, as the α-naphthamide derivatives, be chromatographically separated on a silica-bonded chiral stationary phase.[1,2] Such separations provide the basis for sensitive and accurate determinations of enantiomeric purity and absolute configuration as well as a means of preparative resolution. The chiral stationary phase (CSP) employed, **1**, is derived



1

from (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine and is commercially available.[3,4] A variety of achiral acylating agents can be used to derivatize chiral amines to provide amides resolvable on **1**, α-naphthoyl chloride being used partly for its chromophoric properties. Amides of 1-aryl-1-aminoalkanes resolve particularly well on **1**. To gain insight into the modes of solute–CSP interaction that lead to chiral recognition, we have more closely examined the chromatographic resolution of *N*-acyl-1-aryl-1-aminoalkanes, **2**.



2, Y = alkyl, alkoxy, alkylamino

Table I presents representative data, including elution orders and the signs of $[\alpha]_D$, for the resolution of a series of type **2** amides on CSP **1**. Elution orders were established by chromatographing samples derived from enantiomerically enriched samples of configurationally known amines. Signs of $[\alpha]_D$ were obtained from a polarimetric detector used in tandem with an ultraviolet detector. Figure 1 illustrates a typical chromatogram. Preparative resolution of these amides is feasible, one such being described in the Experimental Section.

To summarize the data in Table I, an increase in either the π basicity of the aryl group or in the size of the alkyl substituent will enhance chiral recognition, whereas an increase in the length of the alkyl "tail" of the acyl group diminishes chiral recognition.[5] For all configurationally known compounds in Table I, the *S* enantiomers are last eluted from (*R*)-**1**.

The experimental observations may be rationalized by a chiral recognition model somewhat like that used to account[1] for the resolution on **1** of the α-naphthamides of amines of structure $R_1CHNH_2R_2$. Following our usual

(1) Pirkle, W. H.; Finn, J. M.; Hamper, B. C.; Hyun, M. H.; Schreiner, J. L.; Pribish, J.; Sowin, T. J.; Welch, C. J., paper presented at the Symposium on Molecular Interactions in Chemical Separations: Solutes, Solvents, and Surfaces, 184th ACS National Meeting, Kansas City, Missouri, Sept 1982.

(2) Pirkle, W. H., paper presented at the Midwest Regional Meeting of the Academy of Pharmaceutical Sciences, Chicago, Illinois, May 23, 1983.

(3) The column used is a commercial version (Regis Chemical Co.) of our earlier reported[4] CSP. Rather similar results can be obtained with the ionically bonded version of this CSP,[6] which is available from Regis and from J. T. Baker Chemical Co.

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

(5) The extent of chiral recognition is gauged by the magnitude of α, the separability factor for the enantiomers.

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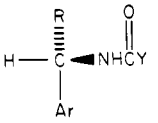
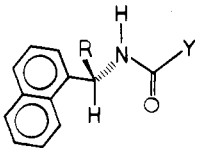
Table I. Resolution of *N*-Acyl-1-arylaminoalkenes on Chiral Stationary Phase 1



Ar	R	Y	α[a]	κ_1'[b]	config[c]	$[\alpha]_D$[d]
phenyl	CH_3	H	1.14	6.8	*S*	–
	C_2H_5	H	1.15	2.9	*S*	–
	i-C_3H_7	H	1.20	2.5	*S*	–
	CH_3	CH_3	1.15	4.9	*S*	–
	C_2H_5	CH_3	1.22	3.9	*S*	–
	i-C_3H_7	CH_3	1.30	3.2	*S*	–
p-anisyl	CH_3	CH_3	1.25	9.5	*S*	–
1-naphthyl	CH_3	CH_3	1.86	8.1	*S*	–
		C_2H_5	1.73	6.7	*S*	
		n-C_3H_7	1.71	5.4	*S*	
		n-C_6H_{13}	1.42	3.7	*S*	
		n-$C_{11}H_{23}$	1.38	3.7	*S*	–
		OCH_3	1.52	3.5	*S*	–
		OC_2H_5	1.44	2.6	*S*	–
		$NHCH_3$	2.03	7.0	*S*	–
		NH-*n*-C_4H_9	1.44	6.4	*S*	
		CF_3	1.40	2.2	*S*	–
	i-C_3H_7	CH_3	2.20	6.2		–
		n-C_3H_7	1.95	5.2		–
		n-$C_{11}H_{23}$	1.40	2.1		–
		OCH_3	1.60	2.3		–
		OC_2H_5	1.42	1.7		–
		$NHCH_3$	2.38	10.6		–
		NH-*n*-C_4H_9	1.33	6.4		–
		CF_3	1.36	1.6		–
2-naphthyl	CH_3	CH_3	1.76	9.8	*S*	–
		n-C_3H_7	1.53	7.3	*S*	–
		n-$C_{11}H_{23}$	1.17	4.5	*S*	–
6,7-$(CH_3)_2$-1-naphthyl	CH_3	CH_3	2.20	10.3		–
		n-C_3H_7	1.50	6.0		–
		n-$C_{11}H_{23}$	1.40	5.2		–
	i-C_3H_7	CH_3	2.40	4.1		+
		n-$C_{11}H_{23}$	1.39	1.6		+
	c-C_6H_{11}	CH_3	3.08	5.0		+
		n-C_3H_7	2.14	3.6		+
		n-$C_{11}H_{23}$	1.96	1.6		+
6,7-$(CH_3)_2$-2-naphthyl	*i*-C_3H_7	CH_3	3.02	7.3		–
		n-$C_{11}H_{23}$	1.73	2.5		–

[a] Chromatographic separability factor. [b] Capacity factor for the first eluted enentiomer using 10% 2-propanol in hexane as a mobile phase. [c] Absolute configuration of the most strongly retained enantiomer. This configuration is depicted in the generalized structure at the top of the table. [d] Sign of $[\alpha]_D$ of the most strongly retained enantiomer as determined by a polarimetric HPLC detector. This is the sign of $[\alpha]_D$ of the amide, not the amine precursor, in 10% 2-propanol-hexane.

practice, we will utilize the conformations expected to be most stable *in solution*.[6-8] These are depicted in **1** and **3**.



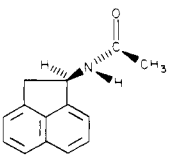
3

The salient conformational feature of the CSP is that the *Z* rotamer of the 3,5-dinitrobenzamide (DNB) portion of the molecule is preferentially populated and is incorporated into a semirigid molecular backbone, the aminyl hydrogen on the chiral center being essentially eclipsed *on a time-average basis* with the DNB carbonyl oxygen as shown in **1**. From one face of this backbone projects a large phenyl group and from the other projects a smaller carboxamide group.

We choose to illustrate solute conformation by using an α-naphthyl system.[9] This system has appreciable conformational control (engendered by its peri hydrogen) and is of obvious π basicity. In *N*-acyl-1-(1-naphthyl)-1-

(6) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1981**, *46*, 2935.
(7) Pirkle, W. H.; Schreiner, J. L. *J. Org. Chem.* **1981**, *46*, 4988.
(8) Pirkle, W. H.; Finn, J. M.; Hamper, B. C.; Schreiner, J.; Pribish, J. R. In "Asymmetric Reactions and Processes in Chemistry"; Eliel, E. L., Otsuka, S.; Eds.; American Chemical Society: Washington, DC, 1982; *ACS Symp. Ser.* No. 185, Chapter 18.

(9) Although the 1-naphthyl system is used in this description, these arguments are intended to extend to other aryl systems as well. However, conformation is extremely important to chiral recognition, and systems lacking the conformational control of the 1-naphthyl system or preferentially adopting conformations different than those described may not behave as expected on the basis of the present model. For example, the acetamide of 9-aminoacenaphthalene, **4**, shows much less chiral recognition (α 1.17) on **1** than does the acetamide of 1-(1-naphthyl)ethylamine (α 1.86). The elution order of the former is not yet known, and owing to the conformational dissimilarity of the two amides, we make no claim that the present model accounts for the elution order of **4**.



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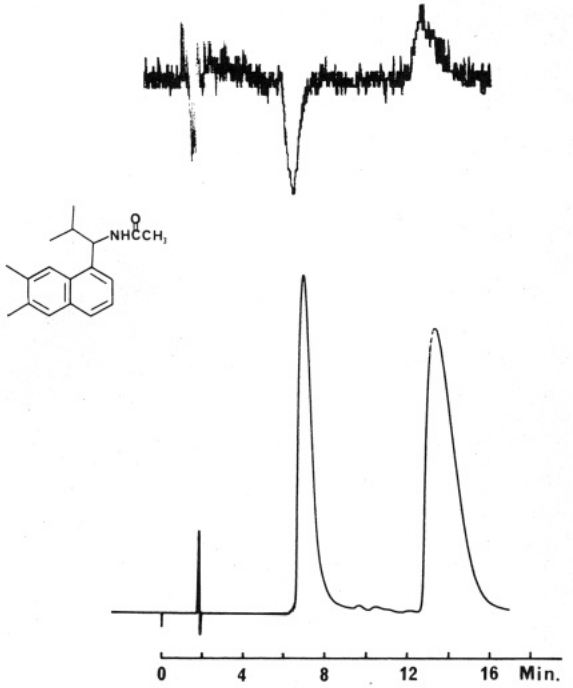
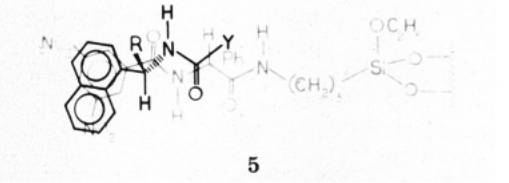


Figure 1. Chromatographic separation of the enantiomers of *N*-acetyl-1-(6,7-dimethyl-1-naphthyl)-1-amino-2-methylpropane on CSP **1**. The upper trace is optical rotation (589 nm), the lower is ultraviolet adsorption (254 nm). The 4.6 × 250 mm column used here was supplied by the J. T. Baker Chemical Co. The flow rate (2.0 mL/min) and sample size are both greater than optimal in terms of column efficiency. Mobile phase was 10% 2-propanol in hexane and the pressure was ca. 1000 psi. The chromatographic separability factor, α, is the ratio of the retention times of the enantiomers measured from the emergence of a nonretained solute. The ratio here is ca. 2.2. The amplitude of the polarimetric response for the first enantiomer is ca. −0.010°; the ultraviolet response is ca. 0.4 au.

aminoalkanes, **3**, the aminyl hydrogen, as the smallest of the three substituents on the chiral carbon, is held close to the peri hydrogen and is, on a time-average basis, essentially in the plane of the 1-naphthyl system.[10] The dihedral angle between the aminyl hydrogen and the hydrogen on the amide nitrogen is ca. 180°. Thus the carboxamide group is relatively fixed in its orientation to the α-naphthyl system.

Chiral recognition requires at least three simultaneous interactions between the CSP and a solute enantiomer, one or more of these interactions being stereochemically dependent. For this particular CSP and solute combination, a variety of possible interactions seems probable. Prior workers concerned with the chromatographic resolution of enantiomeric amides have considered hydrogen bond formation as essential to chiral recognition. While this may sometimes be the case, one need not invoke hydrogen bond formation to rationalize the present results. For example, we suggest that chiral recognition involves an antiparallel alignment of the dipoles associated with the amide groups, causing solute molecules to "stack" preferentially onto the most accessible (i.e., the carboxamide) face of the CSP. Simultaneous π–π interaction between the DNB group and the α-naphthyl system gives rise to the transient adsorbate shown in **5**. By using space-filling models, it may be seen that these interactions occur most readily for the enantiomer shown in **5**. Hence, the enantiomer depicted in

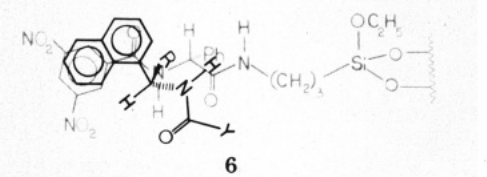


5

5 is expected to be the most strongly retained by (*R*)-**1**.[12] This is the elution order observed for all cofigurationally known amides in the table. Were the other enantiomer to enjoy these same bonding interactions, it would have to assume a conformation that crowds the R group against the peri hydrogen (imagine that R and the aminyl hydrogen in **5** are interchanged). This would be a higher energy adsorbate than is **5**. The larger the R group, the greater the energy difference between the diastereomeric adsorbates and the larger the magnitude of α.

Because of the mode in which these acylated amines are proposed to "stack" onto the CSP, the model suggests that the alkyl "tail" of the acyl group must intercalate between the strands of bonded phase and be directed toward the silica support. This intercalation would presumably lead to an unfavorable steric interaction between the alkyl "tail" and the silica. The longer the "tail" the more severe the interaction and the less this mechanism contributes to the overall retention process.[13] Experimentally, one notes that an increase in "tail-length" diminishes the magnitude of α, the separability factor.

A variation on model **5** is shown in **6**. Only a slight



6

repositioning of the "stacked" solute seems necessary to allow the DNB amide hydrogen to bond to the carbonyl oxygen of the solute. In effect, the major difference between **5** and **6** is that the latter utilizes a hydrogen bond instead of dipole stacking. Both models, to the extent that they can be considered different and not just two formal representations of one intermediate situation, lead to the same expectations concerning elution order and effect of tail length. The second model also allows one to more clearly anticipate the effect of electronegative acyl groups such as trifluoroacetyl; both retention and chiral recognition are diminished substantially as the basicity of the carbonyl oxygen is reduced. Additionally, one might expect that carbamates and ureas derived from 1-arylalkylamines would also resolve, that they would elute in the same order and show the same general behavioral trends as do the corresponding amides. This expectation is realized (Table I).

Despite the ability of the preceding models to rationalize the data in the table, it must be emphasized that the combination of functionality present in these solutes and CSP **1** would seem, from study of space-filling molecular models, to make possible other chiral recognition mechanisms. At present, it seems unnecessary to invoke other

(10) Note that this is not the conformation populated by crystalline *N*-acetyl-1-(1-naphthyl)ethylamine.[11]

(11) Weinstein, S.; Feibush, B.; Gil-Av, E. *J. Chromatogr.* **1976**, *126*, 97.

(12) It is the *shape* of the enantiomer that determines elution order and not whether it is designated *R* or *S* by a stereochemical convention in which assignments are influenced by the priorities of the substituents as well as by absolute configuration.

(13) This suggestions is made principally on the basis of the steric repulsion expected to occur between the alkyl tail and the silica support. Apart from this, intercalation might otherwise be energetically favorable owing to weak van der Waals interactions between the hydrocarbon portions of the solute "tail" and the CSP's connecting "arm". These interactions might become significant in aqueous mobile phases.

hypothetical models to explain the observed data. However, chromatography, like NMR, gives a weighted time-averaged view of events. Hence, changes in solute structure, by altering the balance between competing chiral recognition mechanisms, may afford behavior unexpected on the basis of the preceding models.[14] Diminished π basicity of the aryl system,[15] altered conformational behavior, or inclusion of additional polar functional groups that interact with the CSP would seem to be likely perturbing influences. It is even conceivable that changes in mobile-phase composition might bring about significant changes in the balance point between competing chiral recognition mechanisms although this has not been observed for 1.

Our intent in issuing these caveats is to prevent unthinking application of this (or any other) chiral recognition model without regard for the limitations and requirements of that model. In point of fact, we think that the absolute configurations of all the amides in the table can be assigned on the basis of elution order from CSP 1 and we assign the *S* configuration to the most strongly retained enantiomers of the heretofore configurationally unassigned amides in the table.

Finally, we point out that an additional application for the chiral recognition model is that it is able to provide insight into the design elements needed for a "reciprocal" type 3 CSP if it is to efficiently separate the enantiomers of amines, amino alcohols, and amino acid derivatives, all as the 3,5-dinitrobenzamides. Such CSP's will be the subject of a subsequent paper.

Experimental Section

Chromatography was performed with a Beckman A-100 pump, 210 injector, and Model 165 variable-wavelength detector. A Rudolph[16] Autopol III with a 20-cm flow cell was used to monitor $[\alpha]_D$. The column employed is a 4.6 × 250 mm Regis Covalent Pirkle-1A.

Most of the solutes used in this study are unexceptional in their preparation in that they are derived from acylation of well-known configurationally established amines.[17] These amines were commercial in origin or were available from prior studies. Representative procedures are given for the preparation of several heretofore unreported amines.

The amides used in this study were prepared by treating a methylene chloride solution of the amine with a slight excess of an acyl chloride. The solution was washed sequentially with 2 M sodium hydroxide, 2 M hydrochloric acid, and water and then dried and filtered prior to injection. The amounts injected varied according to the chromophoric properties of the solutes but were always small enough so as to not influence κ' and α. The polarimetric detector, being less sensitive than the ultraviolet detector, usually required a second run using a larger sample (ca. 1 mg). The amplitude of the rotations produced was 5–25 millidegrees.

6,7-Dimethyl-1-naphthyl Isopropyl Ketone. Anhydrous aluminum chloride (1.5 g, 0.011 mol) was suspended into 20 mL of methylene chloride, and then isobutyryl chloride (1.2 g, 0.011 mol) was added in one portion. This heterogeneous solution became clear as it was stirred at room temperature for 10 min. After the acylating mixture was cooled to 0 °C, 2,3-dimethylnaphthalene (1.56 g, 0.01 mol) in 10 mL of methylene chloride was added dropwise with stirring. The solution was further stirred at 0 °C for 2 h and then poured onto ice. Concentrated HCl was added slowly with stirring until two layers were visible. The organic layer was separated, washed with water, saturated sodium bicarbonate solution, and water, and then dried over anhydrous $MgSO_4$. Solvent was removed under reduced pressure to yield a brown viscous oil. Pure α ketone was obtained as a pale yellow liquid in 55% yield (1.25 g) by medium-pressure liquid chromatography on silica gel using 1:1 methylene chloride–hexane as eluent: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 6 H), 2.39 (s, 3 H), 2.41 (s, 3 H), 3.45–3.53 (m, 1 H), 7.35 (t, 1 H), 7.58 (s, 1 H), 7.62 (d, 1 H), 7.80 (d, 1 H), 8.11 (s, 1 H); IR (neat) cm^{-1} 3052, 2970, 2928, 2868, 1687, 1595, 1570. Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.87; H, 7.85.

6,7-Dimethyl-2-naphthyl Isopropyl Ketone. This ketone was isolated (0.57 g, 25% yield) from the preceding reaction and chromatography. It elutes after the 1-naphthyl isomer: mp 85–87 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 6 H), 2.45 (s, 6 H), 3.67–3.75 (m, 1 H), 7.62 (s, 1 H), 7.71 (s, 1 H), 7.77 (d, 1 H), 7.93 (d, 1 H), 8.37 (s, 1 H); IR (KBr) cm^{-1} 2982, 2940, 1677, 1630. Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.93; H, 7.78.

6,7-Dimethyl-1-naphthyl Cyclohexyl Ketone. This ketone was prepared and isolated in a manner analogous to that described above: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.0–1.9 (m, 10 H), 2.39 (s, 3 H), 2.41 (s, 3 H), 3.18 (m, 1 H), 7.15 (t, 1 H), 7.54 (s, 1 H), 7.62 (d, 1 H), 7.79 (d, 1 H), 8.07 (s, 1 H); IR (KBr) cm^{-1} 2870, 1670, 1610. Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.33. Found: C, 85.47; H, 8.11.

α-(6,7-Dimethyl-1-naphthyl)isobutylamine. A solution of 6,7-dimethyl-1-naphthyl isopropyl ketone (1.18 g, 0.0052 mol), ammonium acetate (4.72 g, 0.061 mol), and sodium cyanoborohydride (1.18 g, 0.019 mol) in 20 mL of methyl alcohol was stirred at reflux for 48 h. After cooling, concentrated HCl was added to the mixture (pH <2), and methyl alcohol was removed under reduced pressure. To the aqueous residue was added 20 mL of water, and the solution was twice extracted with ether. The aqueous layer was made basic with KOH pellets and extracted twice with 40-mL portions of ether. The last two ethereal extracts were combined, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to give a pale yellow liquid (1.15 g, 50%): ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3 H), 1.03 (d, 3 H), 1.53 (br s, 2 H), 1.94–2.33 (m, 1 H), 2.43 (s, 3 H), 2.49 (s, 3 H), 4.45 (d, 1 H), 7.20–7.87 (m, 5 H). When 2 drops of D_2O were added, the broad peak at 1.53 ppm disappeared: IR (neat) cm^{-1} 3365, 3282, 3050, 3000, 2950, 2915, 2860, 1650 (w), 1596 (w); high resolution-mass spectrum, calcd for $C_{16}H_{21}N$ 227.1674, found 227.1667.

α-(6,7-Dimethyl-2-naphthyl)isobutylamine. This amine was prepared, as described above, by reductive amination of the corresponding ketone: ^{1}H NMR ($CDCl_3$) δ 0.80 (d, 3 H), 1.01 (d, 3 H), 1.50 (br s, 2 H), 1.77–2.03 (m, 1 H), 2.40 (s, 6 H), 3.70 (d, 1 H), 7.20–7.70 (m, 5 H). When 2 drops of D_2O were added, the broad singlet at 1.50 ppm disappeared: IR (neat) cm^{-1} 3370, 3300, 3050, 3007, 2958, 2870, 1610, 1504; high-resolution mass spectrum, calcd for $C_{16}H_{21}N$ 227.1674, found 227.1663.

Cyclohexyl(6,7-dimethyl-1-naphthyl)methylamine. This amine was prepared and isolated as described above: ^{1}H NMR ($CDCl_3$) δ 1.00–1.83 (m, 13 H), 2.45 (s, 3 H), 2.50 (s, 3 H), 4.50 (d, 1 H), 7.20–7.87 (m, 5 H). When 2 drops of D_2O were added, the number of protons in the 1.00–1.83-ppm region was reduced to 11: IR (neat) cm^{-1} 3380, 3310, 3055, 3003, 2920, 2850, 1600, 1500; high-resolution mass spectrum, calcd for $C_{19}H_{25}N$ 267.1987, found 267.1985.

***N*-(10-Undecenoyl)-α-(6,7-dimethyl-1-naphthyl)isobutylamine.** This amide was prepared from the amine by the action of 10-undecenoyl chloride: mp 65–67 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 3 H), 1.00 (d, 3 H), 1.23 (br s, 10 H), 1.37–1.73 (m, 2 H), 1.90–2.27 (m, 5 H), 2.37 (s, 3 H), 2.42 (s, 3 H), 4.80–5.03 (m, 2 H), 5.47–6.00 (m, 3 H), 7.23 (d, 2 H), 7.47–7.63 (m, 2 H), 7.90 (s, 1 H); IR (KBr) cm^{-1} 3310, 2928, 2855, 1640, 1540. Anal. Calcd for $C_{27}H_{39}NO$: C, 82.39; H, 9.99; N, 3.56. Found: C, 82.30; H, 10.20; N, 3.28.

The racemic amide (6 g) was resolved on a previously described[18] chiral preparative column using 2% isopropyl alcohol

(14) Alternate chiral recognition schemes may operate in either the same sense (e.g., the model in ref 1) or in a sense opposite to the present model. "Opposite sense" mechanisms, should they become dominant, would lead to unexpected elution orders.

(15) Diminished π basicity may stem either from actual reduction in π basicity or a change in the shape or location of the π base so that it less effectively undergoes simultaneous π–π interaction and dipole stacking.

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in *n*-hexane as a mobile phase. High-R_f enantiomer: mp 70.0–73.0 °C; $[\alpha]_D$ −35.4° (*c* 0.54, CH_2Cl_2). Low-R_f enantiomer: mp 71.0–73.5 °C; $[\alpha]_D$ +39.0° (*c* 0.8, CH_2Cl_2).

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Registry No. (*S*)-**2** (Ar = phenyl; R = CH_3; Y = H), 19145-06-3; (*S*)-**2** (Ar = phenyl; R = C_2H_5; Y = H), 87858-37-5; (*S*)-**2** (Ar = phenyl; R = *i*-C_3H_7; Y = H), 87858-38-6; (*S*)-**2** (Ar = phenyl; R = CH_3; Y = CH_3), 19144-86-6; (*S*)-**2** (Ar = phenyl; R = C_2H_5; Y = CH_3), 20306-86-9; (*S*)-**2** (Ar = phenyl; R = *i*-C_3H_7; Y = CH_3), 62474-74-2; (*S*)-**2** (Ar = *p*-anisyl; R = CH_3; Y= CH_3), 82776-14-5; (*S*)-**2** (Ar = 1-naphthyl; R = CH_3; Y = CH_3), 82796-68-7; (*S*)-**2** (Ar = 1-naphthyl; R = CH_3; Y = C_2H_5), 87782-87-4; (*S*)-**2** (Ar = 1-naphthyl; R = CH_3; Y = *n*-C_3H_7), 87782-88-5; (*S*)-**2** (Ar = 1-naphthyl; R = CH_3; Y = *n*-C_6H_{13}), 87782-89-6; (*S*)-**2** (Ar = 1-naphthyl; R = CH_3; Y = *n*-$C_{11}H_{23}$), 61761-45-3; (*S*)-**2** (Ar = 1-naphthyl; R = CH_3; Y = OCH_3), 87782-90-9; (*S*)-**2** (Ar = 1-napthyl; R = CH_3; Y = OC_2H_5), 87782-91-0; (*S*)-**2** (Ar = 1-naphthyl; R = CH_3; Y = $NHCH_3$), 87782-92-1; (*S*)-**2** (Ar = 1-naphthyl; R = CH_3; Y = NH-*n*-C_4H_9), 87801-35-2; (*S*)-**2** (Ar = 1-naphthyl; R = CH_3; Y = CF_3), 66964-33-8; (−)-**2** (Ar = 1-naphthyl; R = *i*-C_3H_7; Y = CH_3), 87782-93-2; (−)-**2** (Ar = 1-naphthyl; R = *i*-C_3H_7; Y = *n*-C_3H_7), 87782-94-3; (−)-**2** (Ar = 1-naphthyl; R = *i*-C_3H_7; Y = *n*-$C_{11}H_{23}$), 87782-95-4; (−)-**2** (Ar = 1-naphthyl; R = *i*-C_3H_7; Y = OCH_3), 87782-96-5; (−)-**2** (Ar = 1-naphthyl; R = *i*-C_3H_7; Y = OC_2H_5), 87782-97-6; (−)-**2** (Ar = 1-naphthyl; R *i*-C_3H_7; Y = $NHCH_3$), 87782-98-7; (−)-**2** (Ar = 1-naphthyl; R = *i*-C_3H_7; Y = NH-*n*-C_4H_9), 87782-99-8; (−)-**2** (Ar = 1-naphtyl; R = *i*-C_3H_7; Y = CF_3), 87783-00-4; (*S*)-**2** (Ar = 2-naphthyl; R = CH_3; Y = CH_3), 87783-01-5; (*S*)-**2** (Ar = 2-naphthyl; R = CH_3; Y = *n*-C_3H_7), 87783-02-6; (*S*)-**2** (Ar = 2-naphthyl; R = CH_3; Y = *n*-$C_{11}H_{23}$), 87783-03-7; (−)-**2** (Ar = 6,7-dimethyl-1-naphthyl; R = CH_3; Y = CH_3), 87783-04-8; (−)-**2** (Ar = 6,7-dimethyl-1-naphthyl; R CH_3; Y = *n*-C_3H_7), 87783-05-9; (−)-**2** (Ar = 6,7-dimethyl-1-naphthyl; R = CH_3; Y = *n*-$C_{11}H_{23}$), 87783-06-0; (+)-**2** (Ar = 6,7-dimethyl-1-naphthyl; R = *i*-C_3H_7; Y = CH_3), 87783-07-1; (+)-**2** (Ar = 6,7-dimethyl-1-naphthyl; R = *i*-C_3H_7; Y = *n*-$C_{11}H_{23}$), 87783-08-2; (+)-**2** (Ar = 6,7-dimethyl-1-naphthyl; R = *c*-C_6H_{11}; Y = CH_3), 87783-09-3; (+)-**2** (Ar = 6,7-dimethyl-1-naphthyl; R = *c*-C_6H_{11}; Y = *n*-C_3H_7), 87783-10-6; (+)-**2** (Ar = 6,7-dimethyl-1-naphthyl; R = *c*-C_6H_{11}; Y = *n*-$C_{11}H_{23}$), 87783-11-7; (−)-**2** (Ar = 6,7-dimethyl-2-naphthyl; R = *i*-C_3H_7; Y = CH_3), 87783-12-8; (−)-**2** (Ar = 6,7-dimethyl-2-naphthyl; R = *i*-C_3H_7; Y = *n*-$C_{11}H_{23}$), 87783-13-9; isobutyryl chloride, 79-30-1; 2,3-dimethylnaphthalene, 581-40-8; 6,7-dimethyl-1-naphthyl isopropyl ketone, 87783-14-0; 6,7-dimethyl-2-naphthyl isopropyl ketone, 87783-15-1; 6,7-dimethyl-1-naphthyl cyclohexyl ketone, 41284-79-1; α-(6,7-dimethyl-1-naphthyl)isobutylamine, 87783-16-2; α-(6,7-dimethyl-2-naphthyl)isobutylamine, 87783-17-3; cyclohexyl(6,7-dimethyl-1-naphthyl)methylamine, 87783-18-4; *N*-(10-undecenoyl)-α-(6,7-dimethyl-1-naphthyl)isobutylamine, 87783-19-5; 10-undecenoyl chloride, 38460-95-6.

Reactions of Mitomycin C with Potassium Ethyl Xanthate in Neutral Aqueous Solution

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The reaction of the antitumor antibiotic mitomycin C with potassium ethyl xanthate was investigated in neutral aqueous solution in the presence and absence of the reducing agent sodium dithionite. The reductive reaction afforded after reoxidation several lipophilic mitosene derivatives. Information on the isolation and structure elucidation of two of these derivatives which were 1,2-trans-disubstituted mitosenes was given earlier (*J. Am. Chem. Soc.* **1979**, *101*, 7121–7124). The present paper reports the isolation of several 1,2-cis-disubstituted-10-(ethylxanthyl)-7-aminodecarbamoylmitosenes and the structure elucidation of two of them. The total yields of the 1,2-trans- and of the 1,2-cis-substituted mitosenes were nearly equal in the reductive reaction, in marked contrast to acid-catalyzed reactions leading to opening of the aziridine ring of mitomycin C which yield cis/trans product ratios in excess of 3. Incubation of mitomycin C with potassium ethyl xanthate and sodium sulfite in the absence of sodium dithionite at 5 °C for 100 h in neutral aqueous medium afforded an aziridinothiourethane. This compound was chemically converted into a mitosene derivative that contained a 1,2-cis-fused thiazoline ring. In the course of high-field ^1H NMR studies of the new mitosene derivatives and of other known mitosenes, a framework for the determination, in favorable cases, of relative stereochemistry at C_1 and C_2 was developed.

Mitomycin C,[4] **1** (Chart I), is a bioreductively[5] activated or acid-activated[6] antitumor antibiotic that is clinically useful for the palliative treatment of various neoplasms.[7] The chemical reactivity of this antibiotic has been the subject of several recent investigations.[5,6,8–16] These investigations and earlier studies summarized in ref 5 and 7 have shown that while mitomycin C is fairly stable when kept at the oxidation level of a quinone and when kept at near neutral pH, its reduction or its exposure to acidic pH leads to changes in the molecule. Reduction of the quinone chromophore leads to loss of methanol from C_9 and C_{9a},[5,10,17] opening of the aziridine ring with participation of a nucleophile,[14,16] and, in some cases, loss and displacement by sulfur nucleophiles of the carbamoyl group.[14]

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