nornicotine (-)-MTPA salt (~95% *R* enantiomer, from a small-scale resolution) were added to a solution of 5.75 g (25 mmol) of **5** in 40 mL of ethyl acetate, and 3 g (13 mmol) of (-)-MTPA (Sigma Chemical Co.) in 10 mL of ethyl acetate was added with stirring. The mixture was allowed to stand at room temperature for 15 min, after which the crystalline product was collected by filtration, washed with 5 mL of ethyl acetate, and air-dried to give 4.2 g, mp 156–166 °C. This material was combined with 0.7 g of crude product from another run and recrystallized three times from boiling acetonitrile (~10 mL/g) to give 3.5 g (52%) of colorless needles, mp 178–179 °C dec. Analysis of the *N*-(trifluoroacetyl)-(*S*)-prolyl amide by GC indicated an enantiomeric purity of ≥95%. Anal. Calcd for $C_{19}H_{20}N_2O_3BrF_3$: C, 49.47; H, 4.37; N, 6.07. Found: C, 49.84; H, 4.51; N, 6.12.

(*S*)-5-Bromonornicotine (5a) (+)-α-Methoxy-α-(trifluoromethyl)phenylacetate. The filtrate from the initial crystallization of the (-)-MTPA salt above was extracted with 1 N sulfuric acid (2 × 20 mL). The acid extracts were combined, washed with 50 mL of ether, made basic with NaOH, and extracted with methylene chloride (2 × 20 mL). Evaporation of the solvent (rotary evaporator), followed by a bulb to bulb distillation (Kugelrohr oven, 110–120 °C, 0.1 mmHg), provided 3.5 g (15.4 mmol) of colorless liquid enriched in the *S* enantiomer. The distillate was dissolved in 25 mL of ethyl acetate, seeded with (+)-MTPA salt (~95% *S* enantiomer, obtained from a small-scale resolution), and treated with a solution of (+)-MTPA (Sigma Chemical Co.) in 10 mL of ethyl acetate, with stirring. After the solution was left standing for 15 min, the crystallized product was collected by filtration and air-dried to give 3.77 g, mp 162–172 °C. Three recrystallizations from boiling acetonitrile (~10 mL/g) yielded 2.8 g (49%) of colorless needles, mp 178–179 °C dec. GC analysis indicated an enantiomeric purity of ≥95%. Anal. Calcd for $C_{19}H_{20}N_2O_3BrF_3$: C, 49.47; H, 4.37; N, 6.07. Found: C, 49.66; H, 4.56; N, 6.09.

(*S*)-Nornicotine. A suspension of **5a** (+)-MTPA salt (1 g, 2.2 mmol) in 50 mL of ether was vigorously shaken with 20 mL of 1 M KOH in a separatory funnel. The ether layer was separated, washed with 20 mL of 1 M KOH, dried over anhydrous K_2CO_3, and evaporated with a rotary evaporator. The residual oil was dissolved in 20 mL of ethanol containing 0.5 mL of triethylamine and hydrogenated at ~1 atm with 0.2 g of 10% palladium on charcoal using the balloon technique.[22] After 1 h, the mixture was filtered through Celite, and the filter cake was washed with 10 mL of ethanol. The filtrate was poured into 50 mL of 1 M K_2CO_3, which was then extracted with two 50-mL portions of methylene chloride. After washing with 20 mL of saturated aqueous NaCl, the combined extract was dried over anhydrous K_2CO_3, evaporated on a rotary evaporator, and then distilled bulb to bulb (Kugelrohr oven, 65–70 °C, 0.1 mmHg) to give 0.30 g (93%) of colorless liquid, $[\alpha]^{24.5}_D$ -35.2° (*c* 2.27, methanol) and -89.0° (*c* 1.81, dioxane). (*S*)-Nornicotine from tobacco has been reported to have $[\alpha]^{21}_D$ -38.3° (*c* 6.07, methanol),[4] $[\alpha]^{24}_D$ -81.6° (*c* 6.73, dioxane),[4] and $[\alpha]^{23}_D$ -88.8° (neat).[2] A small portion was converted to the picrate, which was recrystallized from 95% ethanol to give fine yellow plates, mp 188.5–189.5 °C (lit.[9] mp 190–191 °C), ≥95% enantiomeric purity by GC.

(*R*)-Nornicotine. A mixture of **5b** (-)-MTPA salt (1 g, 2.2 mmol) and 10 mL of 1 M potassium carbonate was extracted with 25 mL of toluene. The toluene layer was separated, washed with 10 mL of 1 M potassium carbonate, dried over anhydrous potassium carbonate, and, after the addition of 0.5 mL of triethylamine, hydrogenated at ~1 atm with 0.2 g of 10% palladium on charcoal using the balloon technique.[22] After 1 h, the catalyst was removed by filtration through Celite, the filter cake was washed with 10 mL of isopropyl alcohol, and the filtrate was extracted with 20 mL of 1 M potassium carbonate. The organic layer was dried over anhydrous potassium carbonate, concentrated with a rotary evaporator, and distilled bulb to bulb (Kugelrohr oven, 65–75 °C, 0.1 mmHg) to give 0.29 g (89%) of colorless liquid, $[\alpha]^{24}_D$ +88.0° (*c* 1.17, hexane) and +34.9° (*c* 3.78, methanol), lit.[3] $[\alpha]^{26}_D$ +86.3° (neat). The product was homogeneous by TLC (0.25-mm silica gel G, ethyl acetate/methanol/58% aqueous ammonia, 85:10:1), R_f 0.12, identical in R_f with (+)-nornicotine. The R_f of 5-bromonornicotine was 0.38. A small portion of the product was converted to the picrate, which after recrystallization from 95% ethanol (yellow plates) had mp 189–190 °C (lit.[3] mp 190–191 °C). GC analysis of the distilled base indicated an enantiomeric purity of ≥95%.

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(22) Fieser, L. F. "Organic Experiments"; D. C. Heath and Co.: Boston, 1964; p 86.

Reaction of Acyl Azide and Amines. Kinetics and Mechanism

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Acyl azides have been known as effective acylation agents for a long time, particularly for the acylation of amino groups in the preparation of peptides.[1] We report in this paper a study of the kinetics and mechanism of the acylation of various amines by 2-naphthoyl azide in both protic and aprotic solvents.

Results and Discussion

Reaction between 11 different amines and 2-naphthoyl azide proceeded well at room temperature in a one to several hour period. The yields were excellent except for *tert*-butyl amine and are listed in Table I. The general procedures for the preparation and isolation of the substituted 2-naphthamides are reported in the Experimental Section.

Reaction rates were determined spectrophotometrically under pseudo-first-order conditions with excess amine concentration for nine amines. The data are reported in Table II. Cleanly first order dependence on amine concentration was observed in all cases in the protic solvents ethanol and 2-methyl-2-butanol and in the aprotic solvent acetonitrile. The first-order dependence on amine concentration was determined by linear regression of the observed pseudo-first-order rate constants vs. amine concentration (see Table II). Correlation coefficients ranged from 0.9917 to 0.9998 and the intercepts were zero within experimental accuracy. Consequently, the rate law is

$$-\frac{d[\text{acyl azide}]}{dt} = k[\text{acyl azide}][\text{amine}] \qquad (1)$$

for all nine amines, both primary and secondary, in all three solvents.

Activation enthalpies and entropies for the reaction with *n*-butylamine and cyclohexylamine in ethanol solution are listed in Table III. Jencks and Gilchrist[2] found an enthalpy and entropy of activation of 8.50 kcal M^{-1} and -32.4 eu, respectively, for the uncatalyzed portion, i.e., the bimolecular term, for the somewhat related reaction of

(1) Lwowski, W. In "The Chemistry of the Azido Group"; Patai, S., Ed.; Interscience: New York, 1971; Chapter 9.
(2) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1966**, *88*, 104.

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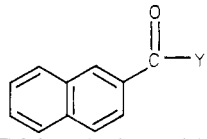
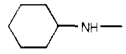
Table I. Percentage Yields of Substituted 2-Naphthamides

amide no.	Y of 	mp, °C	% yield in ethanol by isolation	% yield in 2-methyl-2-butanol by GC	% yield in acetonitrile by GC
1	n-C_4H_9NH-	116-116.5	78	95	96
2	t-C_4H_9NH-	156.5-157.5	<50	98	95
3	$CH_3CH_2CH(CH_3)CH_2NH$-	98-98.5			98
4		183-184[a]	87	72[b]	93
5	$CH_3OCH_2CH_2NH$-	99-100			98
6	$PhCH_2CH_2NH$-	133-134	91	79[b]	94
7	$PhCH_2CH_2CH_2NH$-	99-100	89	76[b]	96
8	$(C_2H_5)_2N$-	oil[c]		95	90
9	$(n$-$C_3H_7)_2N$-	oil[c]		97	97
10	$(n$-$C_4H_9)_2N$-	oil[c]		96	92
11		75.5-76.5			97

[a] Lit. mp 185.6-187.0 °C for ^{18}O derivative: White, E. H.; Aufdermarsh, C. A., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 1179. [b] By isolation. [c] Pagani, G.; Baruffini, A.; Borgna, P. *Farmaco, Ed. Sci.* **1974**, *29*, 491, also report oils for these compounds.

Table II. Second-Order Rate Constants for Acylation of Amines by 2-Naphthoyl Azide (2.5 °C)

amine[a]	concn range of amine, 10^3 M	no. of concns[b]	solvent[c]	10^2k,[d] M^{-1} s^{-1}
1	0.427-4.27	9	CH_3CH_2OH	12.7
1	1.00-16.1	9	MB	4.58
1	0.245-2.45	7	CH_3CN	14.4
3	0.892-9.37	7	CH_3CN	7.12
4	1.01-8.11	8	CH_3CH_2OH	1.97
4	2.00-20.0	9	MB	0.333
4	2.87-30.3	7	CH_3CN	2.08
5	2.25-23.9	7	CH_3CN	3.18
6	1.01-10.1	9	CH_3CH_2OH	4.90
6	2.03-16.3	8	MB	1.80
6	0.933-9.33	7	CH_3CN	2.80
7	1.02-10.2	9	CH_3CH_2OH	10.9
7	2.02-14.1	7	MB	3.45
7	0.907-9.07	7	CH_3CN	8.77
8	4.44-45.6	7	CH_3CN	1.61
9	6.99-70.1	7	CH_3CN	0.485
11	0.181	1	CH_3CN	2270[e]

[a] Y-H in Table I. [b] Number of individual concentrations of amine used to determine pseudo-first-order rate constants. [c] Absolute ethanol, MB is 2-methyl-2-butanol. [d] From pseudo-first-order rate constants by linear regression of first-order constants vs. amine concentrations (correlation coefficients range from 0.9917 to 0.9998); initial concentration of 2-naphthoyl azide was 1.50×10^{-5} M in ethanol and CH_3CN solvents and 3.24×10^{-5} M in MB. [e] Approximate.

methylamine with phenyl acetate in aqueous solution.

The data reported in this paper are consistent with a bimolecular substitution mechanism, or with the addition–elimination mechanism common to carboxyl chemistry, for the reaction between amines and 2-naphthoyl azide. No explicit catalysis by a second amine molecule was observed.

Experimental Section

Materials. 2-Naphthoyl azide was prepared by the previous procedure.[3]

The amines were purified as follows. The amine was dried over potassium hydroxide pellets and fractionally distilled in a nitrogen atmosphere protected from moisture and carbon dioxide. The middle fraction was collected and stored over potassium hydroxide and stored in a dessicator. All amines exhibited satisfactory refractive indices and gave only one peak in GC analysis on an SE-30 column.

Ethanol (100%, no denaturant) was used as received. 2-Methyl-2-butanol was treated several times with activated carbon and fractionally distilled. Acetonitrile was dried over phosphorus pentoxide and then over anhydrous potassium carbonate, fractionally distilled under a dry nitrogen atmosphere, and stored over 3 Å molecular sieves.

Table III. Activation Parameters[a] in Ethanol

parameter	n-butylamine 20.0 °C	n-butylamine 30.0 °C	n-butylamine 40.0 °C	cyclohexylamine 20.0 °C	cyclohexylamine 30.0 °C	cyclohexylamine 40.0 °C
10^2k_2,[b] M^{-1} s^{-1}	9.43	13.4	18.4	1.53	2.05	2.86
$\Delta H^{\ddagger}$, kcal M^{-1}		5.50			5.10	
$\Delta S^{\ddagger}$, eu		−44.4			−49.4	
R[c]		0.999			0.9981	

[a] Calculated from slope and intercept of ln (k_2/T) vs. $1/T$. [b] Second-order rate constants; initial concentration of 2-naphthoyl azide, 1.5×10^{-5} M; n-butylamine, 2.66×10^{-3} to 3.34×10^{-3} M; cyclohexylamine, 1.14×10^{-2} M. [c] Correlation coefficient for regression of ln (k_2/T) vs. $1/T$.

Kinetic Procedure. Five microliters of a solution of 2-naphthoyl azide in the appropriate solvent was added to a thermostated (25.0 °C) solution of the amine in the appropriate solvent. Approximately 3–4 mL of the mixture was transferred into 1-cm quartz cuvettes in a thermostated (25.0 °C) compartment of a Gilford 252 spectrophotometer. The progress of the reaction was monitored by taking absorbance readings for at least

(3) Berndt, D. C.; Zuika, M.; Clark, M. S., Jr. *Chem. Ind. (London)* **1965**, 139.

2 half-lives. The wavelengths used were in the range of 230–236 nm for all amines except for diethyl- and di-*n*-propylamines for which a wavelength of 253 nm was used. Kinetic runs were carried out in duplicate. Solutions in acetonitrile were prepared in a glovebag with a dry nitrogen atmosphere.

The pseudo-first-order rate constants were calculated from the absorbance–time data by the method of Swinbourne.[4]

Amides. 2-Naphthoyl azide (0.500 g, 2.54×10^{-3} mol) dissolved in 20 mL of the appropriate solvent was mixed with 5.08×10^{-2} mol of the amine dissolved in 20 mL of the same solvent. The mixture was allowed to stand at room temperature for a period of 1 h to overnight. The solvent was removed under reduced pressure and the residue was dissolved in 25 mL of 1:1 methylene chloride–ethyl ether. The solution was washed twice with 5% hydrochloric acid, then water, 5% sodium bicarbonate, and water, respectively, and dried over anhydrous magnesium sulfate. The mixture was filtered and the solvent removed from the filtrate under reduced pressure. Solid products were purified by recrystallization from 1:1 ethyl ether–petroleum ether (30–60 °C). Liquid products were purified by column chromatography with acid-washed alumina as absorbent and with petroleum ether (30–60 °C), 1:1 petroleum ether–methylene chloride, and methylene chloride in that order as eluents. All amides gave satisfactory C, H, N analyses (Midwest Microlab, Ltd., Indianapolis, IN), NMR spectra, and the correct molecular ion in the mass spectrum.

Determination of Yield by GC. One-half milliliter of a 0.3200 M solution of 2-naphthoyl azide in the appropriate solvent was mixed with approximately 4×10^{-3} mol of the amine and the mixture allowed to stand overnight at room temperature. One-half milliliter of a 0.3200 M solution of an internal standard (triphenylmethane or phenanthrene) was added and the resulting mixture was analyzed by GC with an SE-30 column. Authentic samples of the amines were used for calibration of the GC procedure.

Registry No. 1, 82740-57-6; 2, 82740-58-7; 3, 82740-59-8; 4, 82740-60-1; 5, 82408-27-3; 6, 82740-61-2; 7, 82740-62-3; 8, 13577-84-9; 9, 53463-19-7; 10, 13797-71-2; 11, 82740-63-4; butylamine, 109-73-9; *tert*-butylamine, 75-64-9; 2-methylbutylamine, 96-15-1; cyclohexylamine, 108-91-8; 2-methoxyethylamine, 109-85-3; phenethylamine, 64-04-0; 3-phenylpropylamine, 2038-57-5; diethylamine, 109-89-7; dipropylamine, 142-84-7; dibutylamine, 111-92-2; pyrrolidine, 123-75-1; 2-naphthalenecarbonyl azide, 1208-11-3.

(4) Swinbourne, E. S. *J. Chem. Soc.* **1960**, 2371.

Communications

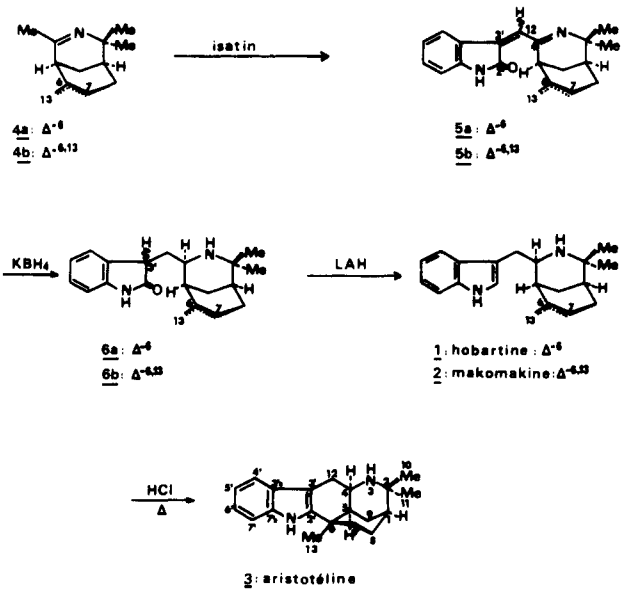
A Synthetic Entry in the *Aristotelia* Alkaloids

Summary: (±)-Hobartine (1) and (±)-aristoteline (3) were prepared from (−)-α-pinene in four and five steps, respectively. In an analogous fashion, (+)-makomakine (2) and (+)-aristoteline (3) were obtained from (−)-β-pinene.

Sir: The *Aristotelia* alkaloids are an emerging class of indole alkaloids that arise from tryptophan and a non-loganin-derived monoterpene unit.[1] Whereas the stepwise assembly of the terpenic part of the molecule would necessarily be lengthy, the recently described mercury-mediated Ritter reactions of acetonitrile with pinenes[2] provide a shortcut to the problem. On the basis of these reactions, we herein describe an expeditious synthesis of hobartine 1,[3] makomakine 2,[4] and aristoteline 3.[5]

Starting material, (±)-**4a**, available in a single step from (−)-α-pinene,[2a,b] was condensed with isatin (EtOH, piperidine, reflux, 30 min) to yield oxindole **5a**[6] (86%; Scheme I), *which contains all the requisite carbon atoms of the target molecules.* The next step in the synthesis demands an adjustment of the oxidation levels at C-2′, C-3′, C-12, and C-4 and a ring closure between C-2′ and C-6. Simultaneous reduction of the unsaturated imine bonds to

Scheme I



6a[7] was achieved with KBH_4; as expected,[2a] reduction of the imine proceeded stereospecifically although a mixture was obtained at C-3′ (46%). This stereospecificity is the result of an axial attack on a six-membered ring and parallels the reduction of similar bicyclic systems.[2] The next step in the synthesis called for conversion of a 3-monosubstituted oxindole to an indole, a reaction that is known to be difficult as a result of the possible enolization to 2-hydroxyindoles.[8] The presence of the terpenic double

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(2) (a) Delpech, B. Thèse de Doctorat ès Sciences Physiques, Université de Paris-Sud, 1977. (b) Delpech, B.; Khuong-Huu, Q. *J. Org. Chem.* **1978**, *43*, 4898–4900. (c) Pancrazi, A.; Kabore, I.; Delpech, B.; Khuong-Huu, Q. *Tetrahedron Lett.* **1979**, 3729–3730.

(3) Kyburz, R.; Schöpp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 2539–2546.

(4) Bick, I. R. C.; Hai, M. A. *Heterocycles* **1981**, *16*, 1301–1302.

(5) (a) Anderson, B. F.; Robertson, G. B.; Avey, H. P.; Donovan, W. F.; Bick, I. R. C.; Bremner, J. B.; Finney, A. J. T.; Preston, N. W.; Gallagher, R. T.; Russel, G. B. *J. Chem. Soc., Chem. Commun.* **1975**, 511–512. (b) Bhakuni, D. S.; Silva, M.; Matlin, S. A.; Sammes, P. G. *Phytochemistry* **1976**, *15*, 574–575.

(6) **5a**: UV (EtOH) λ_{max} 207 nm, 258, 313; IR ($CHCl_3$) 1610, 1625, 1710, 3220 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.40 (s, 6 H), 1.75 (s, 3 H), 2.85 (m, 1 H), 5.42 (m, 1 H), 6.70–7.50 (m, 4 H), 8.40 (m, 1 H), 8.85 (s, 1 H); MS, *m/z* 92, 93 (100), 136, 171, 172, 306 (M^+, 26), 307, 308.

(7) **6a**: UV (EtOH) λ_{max} 211 nm, 250, 281; IR ($CHCl_3$) 1620, 1710, 3220 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.90, 1.02, 1.15, 1.30 (4 s, 6 H), 1.75 (m, 3 H), 5.65 (m, 1 H), 6.70–7.50 (m, 4 H); MS, *m/z* 83, 85, 93, 121, 132, 158, 164, 175, 178, 215, 217, 295, 310 (M^+, 27).

(8) Sundberg, R. J. "The Chemistry of Indoles"; Academic Press: New York, 1973; p 357.

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