14221-01-3; propargylzinc bromide, 106-96-7; triethylamine, 121-44-8; 1,4-diazabicyclo[2.2.2]octane, 280-57-9; sodium amide, 7782-92-5; methylzinc chloride, 5158-46-3; 1-octynylzinc chloride, 68113-72-4; 2-cyclohexenyl acetate, 14447-34-8; benzylzinc bromide, 62673-31-8; 3-benzyl-1-cyclohexene, 4714-10-7; geranyl chloride, 5389-87-7; geranyl tosylate, 33169-56-1; *n*-BuZnCl, 42930-39-2; *i*-BuZnCl, 82510-93-8; *s*-BuZnCl, 74133-06-5; *t*-BuZnCl, 62987-33-1; $LiBEt_3H$, 22560-16-3; *i*-Bu_2AlH, 1191-15-7.

Resolution of (±)-5-Bromonornicotine. Synthesis of (*R*)- and (*S*)-Nornicotine of High Enantiomeric Purity

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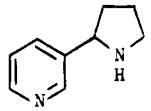
Nornicotine (1) is an alkaloid occurring in tobacco[2] and



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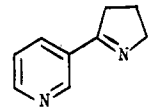

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Duboisia hopwoodii.[3] The alkaloid present in tobacco is levorotatory[2] and has been shown to be a mixture of *R* and *S* enantiomers, with the *S* enantiomer predominating,[4,5] whereas nornicotine from *Duboisia* is the partially racemized *R* isomer.[3] Although racemic nornicotine is readily synthesized on a large scale,[6,7] the enantiomers have been obtained only with difficulty.[8] Both (*R*)- and (*S*)-nornicotine may be obtained from natural sources,[2,3] but the isolation is complicated by the presence of other alkaloids. The synthesis of (*S*)-nornicotine by demethylation of nicotine has been reported; however, the yields were low, and partial racemization occurred.[9] Partially resolved (*S*)-nornicotine has been obtained from the racemate with optically active 6,6′-dinitro-2,2′-diphenic acid as a resolving agent.[10] Unfortunately, the acid is not commercially available and is tedious to synthesize.[11,12] A recent report described an unsuccessful attempt to prepare chiral nornicotine by asymmetric reduction of myosmine (**2**), as well as unsuccessful attempts to resolve racemic nornicotine using a variety of chiral acids.[13] This paper describes an efficient process for the resolution of 5-bromonornicotine. Both isomers are obtained in a high state of enantiomeric purity and may be catalytically debrominated to the corresponding enantiomers of nornicotine without loss of optical purity.

The synthetic route employed is outlined in Scheme I. Preparation of 5-bromomyosmine (**4**) was carried out by base-catalyzed condensation of ethyl 5-bromonicotinate (**3**) with *N*-vinylpyrrolidinone, followed by acid-catalyzed hydrolysis, decarboxylation, and cyclization to **4** during basic workup.[14] Reduction of **4** to 5-bromonornicotine (**5**) was accomplished with sodium borohydride in acetic acid–methanol by a modification of the method of Castonguay and Van Vunakis.[15] Resolution of racemic **5** was attempted with 12 chiral organic acids. Nine produced salts that failed to crystallize or were hygroscopic. Mandelic acid and *O,O′*-dibenzoyltartaric acid gave crystalline salts, but no enantiomeric enrichment was observed on recrystallization. However, the addition of 0.5 equiv of (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(−)-MTPA] to a solution of racemic 5-bromonornicotine in ethyl acetate gave a crystalline salt subsequently shown (see below) to be a 60:40 mixture of *R*/*S* enantiomers. Three recrystallizations from acetonitrile yielded a product that was ≥95% (*R*)-5-bromonornicotine (**5b**). The course of the resolution was readily monitored by GC using the chiral derivatizing agent *N*-(trifluoroacetyl)-(*S*)-prolyl chloride.[16,17] Base-line separation of the resulting diastereomeric amides was obtained on a 2-m SP-2250 column at 260 °C. The mother liquors from the original crystallization of the (−)-MTPA salt, enriched in the *S* enantiomer of 5-bromonornicotine, were converted to the free base and treated with (+)-MTPA to give the crystalline salt, which was ~70% (*S*)-5-bromonornicotine. Three recrystallizations from acetonitrile provided material that was ≥95% *S* enantiomer by GC analysis. Since preparations of the derivatizing agent *N*-(trifluoroacetyl)-(*S*)-prolyl chloride generally contain ~5% of the *R* enantiomer,[18] it is likely that the enantiomeric purity of the resolved 5-bromonornicotine was greater than 95%.

Conversion of the enantiomers of 5-bromonornicotine to the corresponding enantiomers of nornicotine was achieved by reductive debromination with hydrogen and a palladium catalyst. The enantiomer obtained from the (+)-MTPA salt had a specific rotation of −35.2° in methanol, which is in good agreement with the published value of −38.3° for (−)-nornicotine.[4] GC analysis indicated an optical purity of ≥95%. Similarly, the enantiomer obtained from the (−)-MTPA salt was converted into (+)-nornicotine of ≥95% enantiomeric purity. Since (−)-nornicotine has the *S* configuration, it may be inferred that the enantiomers of 5-bromonornicotine obtained from the (+)- and (−)-MTPA salts have the *S* and *R* configurations, respectively.

Nornicotine and 5-bromonornicotine are intermediates in the synthesis of a variety of tobacco alkaloid derivatives of biological interest.[13,15,19] Catalytic reduction of the bromo substituent using deuterium or tritium would provide a simple means for the incorporation of a deuterium or tritium label[20] into a chemically and metaboli-

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(14) This procedure is analogous to a previously reported method for the synthesis of myosmine (see ref 7).

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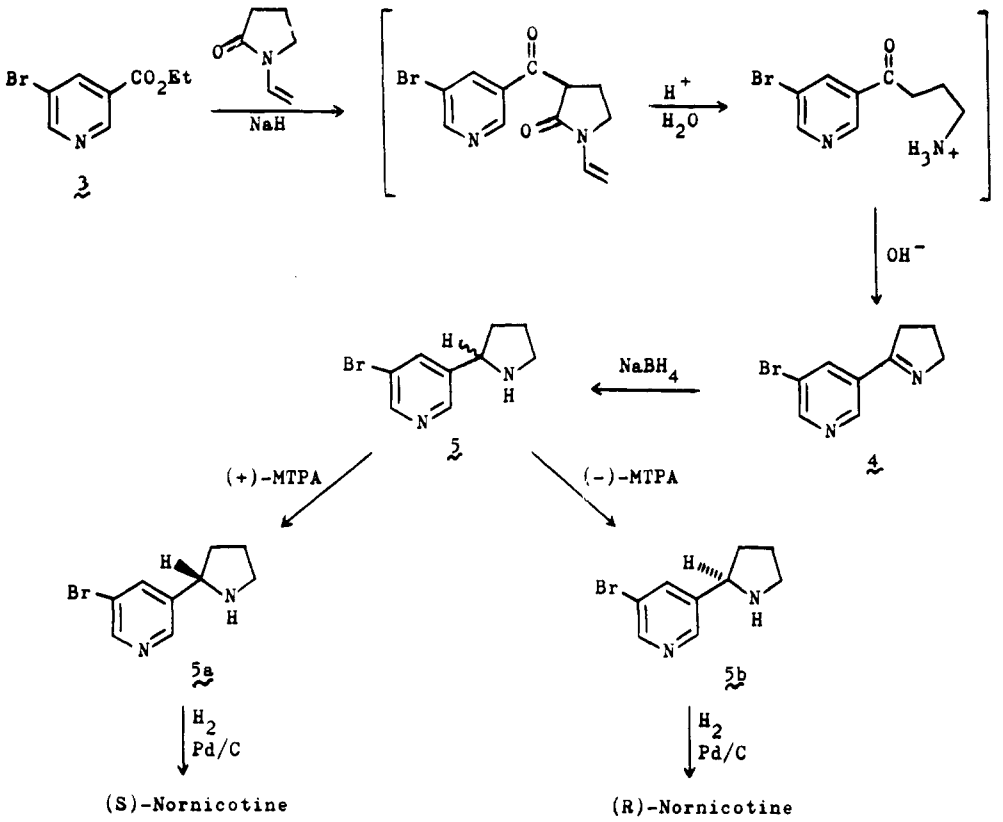
(20) Studies on the preparation of deuterium- and tritium-labeled tobacco alkaloid derivatives are currently being carried out in our laboratory.

0022-3263/82/1947-4165$01.25/0

Scheme I



cally stable[5] position of such derivatives. Consequently, the present development should be valuable in the synthesis of isotopically labeled tobacco alkaloids and related compounds with high optical purity.

Experimental Section

Melting points were taken in capillary tubes with a Mel-Temp (Laboratory Devices) apparatus and are uncorrected. Gas chromatographic analyses were carried out with a Hewlett-Packard 5711A (nitrogen carrier gas, 30 mL/min) or 5880A (helium carrier gas, 30 mL/min) instrument with nitrogen–phosphorus detectors. Optical rotations were obtained with a Perkin-Elmer Model 141 polarimeter or a Jasco DIP-181 digital polarimeter.

5-Bromomyosmine (4).[14] Sodium hydride (12 g of a 50% dispersion in mineral oil, 240 mmol) contained in a 1-L flask was washed free of mineral oil with three 100-mL portions of toluene. The flask was fitted with a reflux condensor, flushed with nitrogen, and charged with 350 mL of THF. A solution of ethyl 5-bromonicotinate (3)[21] (42 g, 180 mmol) and *N*-vinylpyrrolidinone (22 g, 200 mmol) in 50 mL of THF was added in one portion. The mixture was stirred magnetically, and after several minutes an exothermic reaction with vigorous gas evolution commenced. After the exothermic reaction had subsided, the mixture was refluxed for 1 h and then cooled to room temperature. Concentrated HCl (30 mL), diluted with 50 mL of H_2O, was added, and the THF was removed on a rotary evaporator. Additional concentrated HCl (50 mL) and H_2O (100 mL) were added, and the mixture was heated under reflux overnight. The solution was made basic with concentrated aqueous NaOH (ice-bath cooling), which resulted in precipitation of the crude product, and then extracted with methylene chloride (2 × 150 mL). The pooled extracts were washed with H_2O (100 mL), evaporated on a rotary evaporator, and then distilled bulb to bulb [120–140 °C (0.1 mm)] with a Kugelrohr oven to give 26.6 g (66%) of 4, which solidified in the receiver, mp 95–97.5 °C. A small sample that recrystallized from methanol had mp 97.5–98.5 °C (lit[12] mp 98–99 °C).

Racemic 5-Bromonornicotine (5). A modification of the method of Castonguay and Van Vunakis[15] was employed. Sodium borohydride (3.8 g) was added portionwise over 10 min, with vigorous stirring, to a solution of 5-bromomyosmine (10.2 g, 45 mmol) in 100 mL of 80:20 methanol/acetic acid cooled to ~−40 °C with a dry ice–acetone bath. During the course of the addition, the temperature rose to ~−20 °C. After warming to room temperature, most of the solvent was removed with a rotary evaporator. H_2O (250 mL) was added, and the solution was made basic with NaOH and extracted with methylene chloride (2 × 75 mL). The combined extract was washed with 100 mL of saturated aqueous NaCl, dried over anhydrous potassium carbonate, concentrated on a rotary evaporator, and distilled bulb to bulb (Kugelrohr oven, 105–120 °C, 0.1 mmHg) to give 8.05 g (79%) of colorless liquid.

GC Separation of the Enantiomers of 5-Bromonornicotine and Nornicotine as the *N*-(Trifluoroacetyl)-(*S*)-prolyl Amides. To one drop of free base or ~10 mg of the MTPA salt of 5 in a 13 × 100 mm culture tube was added 0.5 mL of 0.1 M *N*-(trifluoroacetyl)-(*S*)-prolyl choride[16,17] in methylene chloride and five drops of triethylamine. The tube was stoppered and mixed briefly, and the solvent was evaporated with a current of air. To the residue were added 1 mL of H_2O and 0.5 mL of toluene, and the contents were agitated on a vortex mixture for a few seconds. The toluene layer was removed, dried over anhydrous K_2CO_3, and analyzed by GC on a 6 ft × 2 mm glass column packed with 3% SP2250 on 100–120 mesh Supelcoport. The retention times of 5-bromonornicotine at 260 °C were 2.8 min for the *R* enantiomer and 3.5 min for the *S* enantiomer. The retention times of nornicotine at 245 °C were 2.6 min for the *R* enantiomer and 3.4 min for the *S* enantiomer.

Attempted Resolutions of (±)-5-Bromonornicotine (5). Salts of the following acids with 5 (1:1 mol ratio) failed to crystallize or were hygroscopic: (+)-tartaric, (−)-quinic, (+)-camphor-10-sulfonic, (+)-camphoric, (+)-orthonitrotartranilic, (−)-menthyl hydrogen succinate, (−)-malic, *N*-acetyl-(+)-cysteine, and *tert*-butyloxycarbonyl-(−)-phenylalanine. Dibenzoyl-(+)-tartaric acid and (+)-mandelic acid gave crystalline salts, but recrystallization failed to produce enrichment in one of the enantiomers. The crude salt obtained from (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(−)-MTPA] was a 60:40 mixture of *R*/*S* enantiomers by GC analysis.

(*R*)-5-Bromonornicotine (5b) (−)-α-Methoxy-α-(trifluoromethyl)phenylacetate. Seed crystals of (*R*)-5-bromo-

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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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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

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