benzene and dried: mp 173 °C, yield 40%; NMR (Me_2SO-d_6) 7.3 (s, 1 H), 3.9 (s, 3 H) ppm; IR (KBr) 3250, 1680, 1500, 1440, 1330, 1200, 1100, 960 cm^{-1}. Anal. Calcd: C, 53.10; H, 4.46. Found: C, 53.04; H, 4.45.

Dimethyl Benzoquinone-2,5-dicarboxylate (1). Dimethyl hydroquinone-2,5-dicarboxylate (**3**) (300 mg, 1.3 mmol) was oxidized in aqueous acetonitrile containing 1.5 equiv of 2,6-di-*tert*-butylpyridine with tetramethylammonium tetrafluoroborate as supporting electrolyte at 1.5 V vs. $Ag/AgNO_3$. After the anodic current dropped to a negligible value, the acetonitrile was evaporated at room temperature which dissolved the organic products and 2,6-di-*tert*-butylpyridinium salts, and the remaining solids were extracted with dichloromethane. Addition of ether precipitated the salts. After rotary evaporation of the filtrate and recrystallization from a dichloromethane/ether mixture at low temperature, orange crystals were obtained: mp 130 °C (yield 30 mg, 10%); NMR ($CDCl_3$) 7.05 (s, 2 H), 3.8 (s, 6 H) ppm; IR (KBr) 3055, 1712, 1666, 1436, 1350, 1271 cm^{-1}; UV (CH_2Cl_2) λ_{max} 255 (3000) nm. Anal. Calcd: C, 53.38; H, 3.60. Found: C, 53.28; H, 3.47.

Acknowledgment. We thank the United States Army Research Office for support of this work under Grant #DAAG 29-82-J-0049 and also Amorn Petsom for carrying out the electrochemical oxidations.

Synthesis of the Enantiomers of Nornicotine

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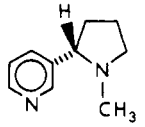
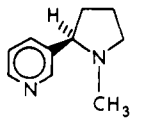
Received April 30, 1985

In the last few years, significant effort has been expended toward the preparation of the enantiomers of nicotine, **1** and **2**, often with the concomitant goal of high



1, (S)-(-)-nicotine

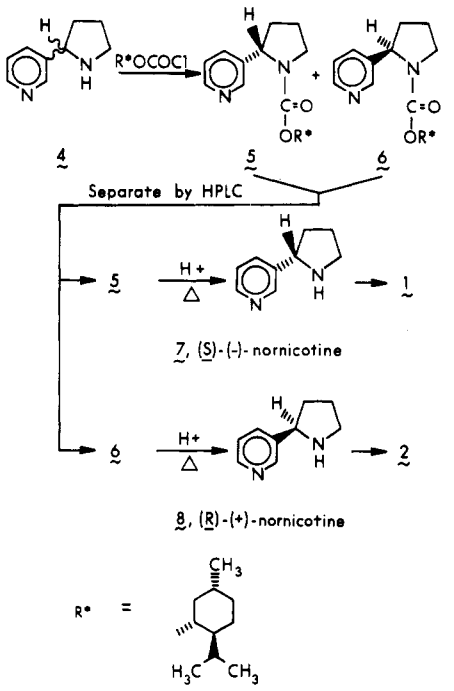


2, (R)-(+)-nicotine

tritium incorporation and high optical purity.[1-4] The preparation of optically pure (*S*)-[^{3}H]nicotine of moderate incorporation (ca. 5–10 Ci/mmol) by tritium reduction of optically pure cotinine dibromide (**3**) has recently been reported.[1] (*R,S*)-[*N-methyl*-^{3}H]Nicotine of high specific activity (>20 Ci/mmol), prepared by the reaction of [^{3}H]iodomethane with (*R,S*)-nornicotine is now available commercially.[5]

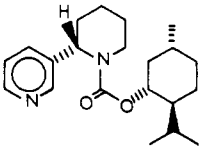
Based on the successful transformation of (*R,S*)-nornicotine to (*R,S*)-[*N-methyl*-^{3}H]nicotine having high specific activity via methylation with [^{3}H]iodomethane,[5,6] we focused our attention toward the development of a general procedure for the preparation of the enantiomers of nornicotine (**7** and **8**).[3] Our successful strategy is illustrated in Scheme I. It depends on the preparative scale formation, separation, and purification of the diastereomeric urethanes **5** and **6**, followed by the hydrolysis of these optically pure urethane diastereomers into their corresponding nornicotine enantiomers **7** and **8** *without* racemization.

Scheme I



The preparation of mixture **5** + **6** from (*R,S*)-nornicotine (**4**) was straightforward and proceeded in high yields by treatment of (*R,S*)-nornicotine[6] with optically pure (–)-menthyl chloroformate. Following much experimentation, we found that the *N'*-(menthoxycarbonyl)nornicotine diastereomers **5** and **6** could be best separated (base-line separation) on a preparative scale using a Whatman Partisil 10, Magnum 20 column with a hexane/acetone/triethylamine (89:11:3) solvent mixture and standard high performance liquid chromatography (HPLC) techniques, as described in detail in the Experimental Section. The HPLC separations were followed by capillary GC analysis and fractions containing urethanes of >99.8% purity were combined for subsequent acid hydrolysis.

Rather than experiment with various hydrolysis conditions with the precious optically active *N'*-(menthoxycarbonyl)nornicotine, we prepared the analogous urethanes **9**[7] from commercially available, optically active (*S*)-(–)-



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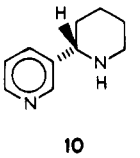

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(4) Edwards, W. B., III; McCuen, R. *J. Org. Chem.* **1983**, *48*, 2484–2487.

(5) The enantiomers of nicotine having high specific activity (60–80 Ci/mmol) have recently become available from New England Nuclear. The New England Nuclear procedure for the preparation of (*R,S*)-[^{3}H]-nicotine involves the methylation of (*R,S*)-nornicotine with [^{3}H]iodomethane (J. Ahern, New England Nuclear, private communication).

(6) Seeman, J. I.; Secor, H. V.; Forrest, G. *J. Labelled Compds. Radiopharm.* **1978**, *16*, 387–395.

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Table I. Specific Rotations for (*S*)-(−)- and (*R*)-(+)-Nornicotine

compound	source	specific rotation $[\alpha]_D$, deg	(°C)	solvent	conc[a]	ref
(*S*)-(−)-nornicotine (7)	tobacco	−38.3	(21)	methanol	6.07	*b*
7	tobacco	−81.6	(24)	dioxane	6.73	*b*
7	tobacco	−88.8	(23)	neat		*c*
7	classical resolution	−35.2	(24.5)	methanol	2.27	*d*
7	classical resolution	−89.0	(24.5)	dioxane	1.81	*d*
7	HPLC of diastereomers	−34.9	(20)	methanol	0.313	this work
7	HPLC of diastereomers	−98.8	(20)	hexane	0.526	this work
(*R*)-(+)-nornicotine (8)	*Duboisia hopwoodii*	+86.3	(24)	neat		*e*
8	*Duboisia hopwoodii*	+26.4	(20)	ethanol	5.8	*f*
8	classical resolution	+34.9	(24)	methanol	3.78	*d*
8	classical resolution	+88.0	(24)	hexane	1.17	*d*
8	HPLC of diastereomers	+34.6	(20)	methanol	0.530	this work
8	HPLC of diastereomers	+99.3	(20)	hexane	0.408	this work

[a] In g/100 mL. [b] Kisaki, T.; Jamaki, E. *Arch. Biochem. Biophys.* **1961**, *92*, 351–355. [c] Späth, E.; Zajic, E. *Chem. Ber.* **1935**, *68B*, 1667–1670. [d] Reference 3. [e] Späth, E.; Hicks, C. S.; Zajic, E. *Chem. Ber.* **1936**, *69B*, 250–251. [f] Luanratana, O.; Griffin, W. J. *Phytochemistry* **1982**, *21*, 449–451.

anabasine (**10**). We examined a number of hydrolytic, hydrogenolytic, and reductive conditions to convert **9** into either optically active anabasine or *N'*-methylanabasine. Base-catalyzed hydrolysis resulted in anabasine with concomitant racemization while attempted hydrogenolysis of **9** led to sizeable quantities of materials in which the pyridine ring was reduced. Fortunately, acid-catalyzed hydrolysis (10% HCl/110 °C) of **9** led to high yields (>80%) of (*S*)-(−)-anabasine having an optical rotation identical with the starting material.

The pure diastereomers **5** and **6** were hydrolyzed to (*S*)-(−)- and (*R*)-(+)-nornicotine (**7** and **8**), respectively, following the acid-catalyzed conditions developed for the hydrolysis of the *N'*-[(menthoxy)carbonyl]anabasine **9**. Table I summarizes the specific rotations obtained for nornicotine from natural sources, from Jacob's recent classical resolution,[3] and from our investigations. In Jacob's resolution of 5-bromonornicotine, he prepared the corresponding amides with the derivatizing agent *N*-(trifluoroacetyl-(*S*)-prolyl chloride which "generally contains ~5% of the *R* enantiomer"[3] and found by GC analysis that the enantiomeric purity of his (*S*)-(−)- and (*R*)-(+)-nornicotine was greater than 95%.

We believe that the nornicotines obtained in our work as shown in Scheme I are >99% optically pure for two reasons: (1) our method relies on the optical purity of the menthyl chloroformate[8] which was prepared from optically pure natural menthol and (2) racemization *does not* occur during acid-catalyzed hydrolysis of the carbamate and *cannot* occur during formation of **5** and **6**, as shown by the recovery of unracemized anabasine in the experiments discussed above.

To place a lower limit on the enantiomeric purity of material obtainable from this procedure, we reconverted both (−)- and (+)-nornicotine separately to their urethane derivative. Capillary gas chromatographic analysis of each of the urethanes indicates that each is >99% optically pure. This is an excellent test for optical purity, in that it provides a cyclic resolution/assay scheme.[9]

In summary, we have reported a convenient procedure for the preparation of the enantiomers of nornicotine in high optical and chemical purity. Given the ready synthesis of racemic [*N-methyl*-^{2}H]nicotine and [*N-methyl*-^{13}C]nicotine from racemic nornicotine,[6] the preparation of essentially optically pure, labeled, and radiolabeled nicotine of high incorporation should be routine.[10,11]

Experimental Section

Melting points and boiling points are uncorrected. The ^{1}H NMR spectra were determined on a Bruker WP-80 or a Varian XL-100 spectrometer. IR spectra were determined on a Perkin-Elmer 735B infrared spectrophotometer. Low resolution mass spectra were obtained on a Finnigan 3300 mass spectrometer. Optical rotations were obtained with a Perkin-Elmer 241 MC polarimeter. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Capillary gas chromatographic analyses were made on a Varian Model 4600 equipped with a DB-5 column (30 m × 0.25 mm i.d.), J & W Scientific, and HPLC separations were made on a Waters 6000A. All GC runs were carried out isothermally at 250 °C. The (*S*)-nornicotine urethane **5** gave a t_R of 7.89 ± 0.04 min and the *R* derivative **6** gave a t_R of 9.12 ± 0.04 min.

(2'*R*,2'*S*)-*N'*-[(1*R*,2*S*,5*R*)-Menthoxycarbonyl]nornicotine (5 + 6). To a solution of 15.0 g (0.101 mol) of nornicotine,[6] 21.2 mL (0.152 mol) of triethylamine, and 500 mL of ether maintained at 0 °C under nitrogen was added a solution of 27.7 g (0.127 mol) of (1*R*,2*S*,5*R*)-menthyl chloroformate over 10 min. The mixture was stirred at 0 °C for 10 min and at room temperature for 1.5 h. Following suction filtration, the ethereal solution was washed with 250 mL of 10% aqueous NaOH, dried ($MgSO_4$), and evaporated to a viscous, dark yellow oil. Two bulb-to-bulb distillations [oven temperature 155–175 °C (0.25 torr)] afforded 29.45 g (88%) of the title compound as a very viscous oil: $[\alpha]^{20}_D$ −57.4° (*c* 1.089, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 8.38–8.63 (m, 2), 7.5 (d of t, *J* = 8, 2 Hz, 1), 7.25 (d of d, *J* = 8.5 Hz, 1), 4.75–5.13 (m, 1), 4.25–4.69 (m, 1), 3.65 (t, *J* = 7 Hz, 2), 0.25–2.75 [m (contains singlets of varying intensity at δ 0.75–0.95), 22].

(7) For the reactivity of anabasine-*N'*-carbonyl chloride, see: Forostyan, Yu. N.; Efimova, E. I.; Oleinik, A. P. *Khim. Prir. Soedin.* **1970**, *6*, 571. See *Chem. Abstr.* **1971**, *74*, 54065w. For an English translation, see: *J. Heterocycl. Chem. U.S.S.R.* **1973**, 587–589 and references cited therein.

(8) (a) The optical purity achievable via this procedure is limited by the care exercised in the HPLC separation of the diastereomers. We note that optically pure (−)-menthyl chloroformate is now commercially available and is listed (Aldrich Chemical Co.) as a reagent to assay optical purity. (b) Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978–3980.

(9) (a) We also attempted to establish the optical purity of **7** and **8** by converting *d,l*-nornicotine to their α-naphthamides and applying the chromatographic separation technique of Pirkle[9b] for enantiomers. Unfortunately, while the enantiomers of the nornicotine α-naphthamides did separate using the Regis Covalent Pirkle-1A column, the resolution was too poor to permit even a crude estimate of optical purity. We did, however, reproduce Pirkle's HPLC separation[9b] of the enantiomers of the α-naphthamides of *d,l-N*-methylpiperidine. (b) Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* **1984**, *49*, 2504–2506.

(10) An alternative approach toward the synthesis of radiolabeled, optically pure nicotine could involve the tritium reduction of an appropriate derivative of optically pure nicotine. For example, Chavdarian[11] has recently reported the synthesis of (*S*)-(−)-3',4'-dehydronicotine of high optically purity which could, in principle, be reduced to radiolabeled (*S*)-(−)-nicotine.

(11) Chavdarian, C. G. *J. Org. Chem.* **1983**, *48*, 1529–1531.

Anal. Calcd for $C_{20}H_{30}N_2O_2$: C, 72.73; H, 9.09; N, 8.48. Found: C, 72.51; H, 9.27; N, 8.41.

Preparative HPLC Resolution of the *N'*-(Menthoxycarbonyl)nornicotine Diastereomers (5 + 6). A semipreparative Whatman Partisil 10 μm Magnum 20 column was employed with hexane/acetone/triethylamine (89:11:3) as the eluent. All separations were carried out at a flow rate of 20 mL/min and monitored by using a refractive index detector. A typical sample size consisted of 300 mg of the diastereomeric carbamate mixture dissolved in 1 mL of the eluent. The first component [precursor of (*R*)-(+)-nornicotine] eluted at approximately 25 min and the separation from the following component was nearly base line. The collected fractions were combined on the basis of purity as determined by capillary gas chromatography analysis. A small amount of a mixed-cut was obtained and was utilized in subsequent purifications. The combined solutions of pure diastereomers obtained from five separations were subjected to vacuum to remove solvent and gave 640 mg of a viscous colorless oil of the first component, (2'*R*)-*N'*-[(1*R*,2*S*,5*R*)-menthoxycarbonyl]nornicotine (**6**): $[\alpha]^{20}_D$ 12.18° (*c* 0.231, CH_2Cl_2). Concentration of the combined fractions of the second component gave 625 mg of colorless crystalline (2'*S*)-*N'*-[(1*R*,2*S*,5*R*)-menthoxycarbonyl]nornicotine (**5**): $[\alpha]^{20}_D$ −135.01° (*c* 0.1985, CH_2Cl_2); mp 61-62 °C.

(*S*)-(−)-Nornicotine (7). A solution of 590 mg of (2'*S*)-*N'*-[(1*R*,2*S*,5*R*)-menthoxycarbonyl]nornicotine (**5**) in 4 mL of 10% HCl was heated in a 25-mL Teflon-lined Parr bomb at 110 °C for 64 h. The reaction vessel was cooled in dry ice and opened without evidence of excess pressure having formed. The reaction mixture was shaken with water and ether, and the resultant aqueous phase was extracted 3 times with ether. The combined ethereal fractions were concentrated under reduced pressure, transferred to a separatory funnel, basified with 50% KOH, and extracted with ether and methylene chloride. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and distilled bulb-to-bulb (65 °C (0.025 torr)) to yield 227 mg (89%) of (*S*)-(−)-nornicotine (**7**) as a colorless mobile oil which had GC, TLC, and spectroscopic properties identical with authentic *d,l*-nornicotine.[6] See Table I for specific rotations.

(*R*)-(+)-Nornicotine (8). A solution of 640 mg (1.939 mmol) of the (+)-carbamate **6** in 4 mL of 10% aqueous HCl was placed in a 25-mL Teflon-lined Parr bomb and heated in the oven at 110 °C for 3 days. The mixture was cooled and then washed with ether (3 × 5 mL). The aqueous layer was basified with concentrated aqueous NaOH and extracted with methylene chloride (3 × 5 mL), and the methylene chloride extracts were combined. The methylene chloride solution was dried ($MgSO_4$) and evaporated to a brown, mobile oil. Bulb-to-bulb distillation (65 °C (0.025 torr)) afforded 213 mg (74%) of (*R*)-(+)-nornicotine (**8**) as a clear, colorless, mobile oil, identical by ^1H NMR, GC, and TLC analyses to authentic *d,l*-nornicotine.[6] See Table I for specific rotations.

Acknowledgment. We thank Dr. Steve Haut for performing some of the initial HPLC separations of the diastereomers **5** + **6**, Ms. Melanie Allgood for carrying out some of the large-scale HPLC preparations and purifications, and Drs. David Douglas, David Ingraham, and Richard Izak for providing technical assistance.

Reductive Dehalogenation of 2,4-Dihalogeno Estrogens Having a 3-Hydroxy Substituent by Formic Acid, Potassium Iodide, or Ascorbic Acid

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Received June 18, 1985

Recently, we[1] developed an efficient synthesis of 2- and 4-methoxy estrogens, the physiologically important estrogen metabolites,[2] via the corresponding halogeno derivatives, in which the preparation of the aromatic A-ring halides is a key step. Mercuric acetate[3] or cupric acetate[4] catalyzed iodination of estrogens gives regiospecifically only the 2-iodo derivatives. Although selective monobromination of estrogens has also been reported,[5] this reaction was unequivocally shown to give an isomeric mixture of 2- and 4-bromo compounds.[6] The brominations so far reported usually lead to nearly equimolar amounts of the two ortho isomers.[1,6,7] We[1] recently discovered the regiospecific hydrodehalogenation of 2,4-diiodo and 2,4-dibromo estrogens by a catalytic hydrogenation with palladium-on-charcoal giving the corresponding 4-halides in very high yields. Pandey and Purkayastha[8] reported a simple method for a hydrodehalogenation of aryl halides by formic acid–dimethylformamide (DMF) in the presence of catalytic amounts of the palladium.

We now describe the hydrodehalogenation of the 2,4-dihalides having a hydroxyl group at the C-3 position with formic acid and other well-known reductants, potassium iodide and ascorbic acid, in DMF in the presence or absence of the palladium. The production of the 2-halides predominates over their 4-isomers under all conditions without the catalyst. In contrast, the 4-halides were regioselectively obtained in modest yields only under the conditions using formic acid and the catalyst.

Table I. Dehalogenation of 2,4-Dihalogeno Estrogens with Formic Acid[a]

substrate	Pd/C	isolated yield,[b] % 2-halide	isolated yield,[b] % 4-halide	2-/4-halide ratio
2,4-dibromides **1a**, **2a**, and **3a**	no	41-57	13-21	2.6-3.6
	yes	5-6	38-45	0.12-0.16
2,4-diiodides **1d**, **2f**, and **3f**	no	40-52	13-20	2.6-3.1
	yes	4-7	35-43	0.11-1.16

[a] DMF, reflux, 3 h. [b] Didehalogenated products were also isolated in 6-10% yields.

Results and Discussion

Reaction of 2,4-dibromo estrogens **1a**, **2a**, and **3a** and 2,4-diiodo derivatives **1d**, **2f**, and **3f** with formic acid was initially explored in the presence or absence of catalytic amounts of 5% palladium-on-charcoal under similar conditions (DMF, reflux) as previously reported.[8] The course of the hydrodehalogenation, which was conveniently followed by thin-layer chromatography (TLC), indicated that after 3 h, the substrates almost completely disappeared. Semi-preparative-scale separations of the products were readily effected by reverse-phase high-performance liquid chromatography (HPLC) on a C_{18} column (mobile phase, MeOH/H_2O). The 2,4-dihalogeno compounds were effi-

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