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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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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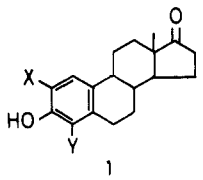
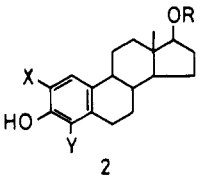
ciently hydrodehalogenated to give the corresponding 2-bromides **1b**, **2b**, and **3b** and 2-iodides **1e**, **2g**, and **3g** as the major products, accompanied with their 4-bromo isomers **1c**, **2d**, and **3d**, and 4-iodo isomers **1f**, **2i**, and **3h** as the minor products, in which the relative amounts of the 2- and 4-halides were between 2.6 and 3.6 (Table I). In



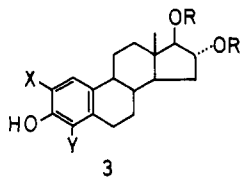
1

a : X = Y = Br
b : X = Br, Y = H
c : X = H, Y = Br
d : X = Y = I
e : X = I, Y = H
f : X = H, Y = I



2

a : X = Y = Br, R = H
b : X = Br, Y = H, R = COH
c : X = Br, Y = H, R = H
d : X = H, Y = Br, R = COH
e : X = H, Y = Br, R = H
f : X = Y = I, R = H
g : X = I, Y = H, R = COH
h : X = I, Y = H, R = H
i : X = H, Y = I, R = COH
j : X = H, Y = I, R = H



3

a : X = Y = Br, R = H
b : X = Br, Y = H, R = COH
c : X = Br, Y = H, R = H
d : X = H, Y = Br, R = COH
e : X = H, Y = Br, R = H
f : X = Y = I, R = H
g : X = I, Y = H, R = H
h : X = H, Y = I, R = H

the experiments using 2,4-dihalogenoestradiol **2a,f** and 2,4-dibromoestriol (**3a**), the products were isolated as the formates, which were subsequently hydrolyzed with sodium bicarbonate back to the corresponding hydroxy derivatives **2c,e,h,j** and **3c,e**, respectively. However, the reaction with 2,4-diiodoestriol (**3f**) gave a complex mixture of products, probably consisting of 16- and 17-monoformates and 16,17-diformates of 2- and 4-iodo derivatives **3g,h**, as indicated by TLC analysis. Then, after alkaline hydrolysis of the crude products, triols **3g,h** were isolated by HPLC. It should be noted that the preferential removal of the C-2 halogen of the 2,4-dihalides by a hydrodehalogenation is reported here for the first time. The regiospecific substitution of the C-2 halogen of the 2,4-dibromides by NO_2 has previously been reported.[9]

In sharp contrast, when catalytic amounts of 5% palladium-on-charcoal were added to the reaction mixtures, 4-halides **1c,f**, **2d,i**, and **3d,h** were regioselectively obtained in 35–45% yields along with small amounts of their 2-isomers (2-/4-halides = 0.11–0.16) (Table I). The results are comparable to those with the catalytic hydrogenation of the 2,4-dihalides.[1]

Treatment of 2,4-dibromides **1a**, **2a**, and **3a** and 2,4-diiodides **1d**, **2f**, and **3f** with potassium iodide (DMF, reflux, nitrogen atmosphere, 6 h) gave 2-bromides **1b**, **2c**, and **3c** and 2-iodides **1e**, **2h**, and **3g** in modest yields along with the corresponding 4-isomers (Table II), in which the ratios of 2- to 4-halides were between 2.0 and 2.5. Addition of the palladium to the reaction mixtures did not cause any

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Table II. Dehalogenation of 2,4-Halogeno Estrogens with Potassium Iodide or Ascorbic Acid[a]

substrate	isolated yield, %[b] 2-halide	4-halide	2-/4-halide ratio
Potassium Iodide Experiment			
2,4-dibromides **1a**, **2a**, and **3a**	27–42	15–18	2.0–2.4
2,4-diiodides **1d**, **2f**, and **3f**	33–48	16–22	2.1–2.4
Ascorbic Acid Experiment			
2,4-dibromides **1a**, **2a**, and **3a**	1	1	
2,4-diiodides **1d**, **2f**, and **3f**	27–35	14–15	2.0–2.5

[a] DMF, reflux, 6 h; the reaction was carried out without 5% palladium-on-charcoal. [b] Didehalogenated compounds were produced in ca. 10% yields except the ascorbic acid–2,4-dibromide experiments. When the catalyst was added to the reaction mixtures, essentially same results were obtained as without the catalyst.

significant changes of the ratios. Reaction of the iodides **1d**, **2f**, and **3f** with ascorbic acid gave essentially the same results as with potassium iodide (Table II). However, the dibromides **1a**, **2a**, and **3a** were not dehalogenated under the conditions but the substrates were recovered in high yields. To our knowledge, a hydrodehalogenation of aromatic halides with potassium iodide and ascrobic acid, so far, has not been reported in the literature.

Experimental Section

General Methods. Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 400 spectrophotometer in KBr pellets. ^1H NMR spectra were obtained with JEOL PMX 60 (60 MHz) spectrometer using tetramethylsilane as an internal standard. High-performance liquid chromatography (HPLC) was carried out on a Waters ALC/PGC 244 liquid chromatograph equipped with a U6K injector and a differential refractometer detector, in which a reverse-phase μ-Bondapak C_{18} column (30 cm × 0.8 cm id) or Erma ERS-ODS column (25 cm × 1.0 cm id) and $MeOH/H_2O$ were employed as the stationary and mobile phases, respectively.

Reaction of 2,4-Dibromo Estrogens 1a, 2a, and 3a and 2,4-Diiodo Derivatives 1d, 2f, and 3f with Formic Acid, Potassium Iodide, or Ascorbic Acid. 2,4-Dihalogeno compounds (1 mmol), synthesized according to the previous reports,[1,9] were dissolved in DMF (5.4 mL). Formic acid (0.33 mL, 8.6 mmol), KI (272 mg, 1.6 mmol), or ascorbic acid (272 mg, 1.5 mmol) was added to the solution, and the mixtures were heated under reflux for an appropriate time in the presence of 5% palladium-on-charcoal (54 mg, 0.5 mmol) or without the catalyst. The reactions with KI and ascorbic acid were carried out under a N_2 atmosphere. The reactions were followed by TLC analysis (silica gel, hexane/AcOEt as solvent). The mixtures were cooled, and the catalysts were removed by filtration and washed with AcOEt (if necessary). The filtrates were diluted with AcOEt (100 mL), washed with aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). After evaporation of the solvent, the residual crude products (200–230 mg) were purified by HPLC to give 2- and 4-halogeno derivatives.[1,3-7]

2-Bromo-1,3,5(10)-estratriene-3,17β-diol 17-formate (2b): mp 203–205 °C (MeOH); yield 57%; IR (KBr) 3440 (OH), 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 4.80 (1 H, t, J = 7 Hz, 17α-H), 6.73 (1 H, s, 4-H), 7.33 (1 H, s, 1-H), 8.13 (1 H, s, 17β-OCOH). Anal. Calcd for $C_{19}H_{21}O_3Br$: C, 60.15; H, 6.06. Found: C, 59.94; H, 5.79.

4-Bromo-1,3,5(10)-estratriene-3,17β-diol 17-formate (2d): mp 184–185 °C (MeOH); yield 45%; IR (KBr) 3440 (OH), 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 4.80 (1 H, t, J = 8 Hz, 17α-H), 6.80 (1 H, d, J = 9 Hz, 2-H), 7.14 (1 H, d, J = 9 Hz, 1-H), 8.13 (1 H, s, 17β-OCOH). Anal. Calcd for $C_{19}H_{21}O_3Br$: C, 60.15; H, 6.06. Found: C, 60.06; H, 5.94.

2-Iodo-1,3,5(10)-estratriene-3,17β-diol 17-formate (2g): mp 190–191 °C (MeOH); yield 52%; IR (KBr) 3400 (OH), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 4.76 (1 H, t, J = 8 Hz, 17α-H), 6.70 (1 H, s, 4-H), 7.50 (1 H, s, 1-H), 8.13 (1 H, s,

17β-OCOH). Anal. Calcd for $C_{19}H_{21}O_3I$: C, 53.52; H, 5.39. Found: C, 53.51; H, 5.29.

4-Iodo-1,3,5(10)-estratriene-3,17β-diol 17-formate (2i): mp 196–197 °C (MeOH); yield 43%; IR (KBr) 3400 (OH), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 4.80 (1 H, t, J = 8 Hz, 17α-H), 6.80 (1 H, d, J = 9 Hz, 2-H), 7.23 (1 H, d, J = 9 Hz, 1-H), 8.13 (1 H, s, 17β-OCOH). Anal. Calcd for $C_{19}H_{21}O_3I$: C, 53.52; H, 5.39. Found: C, 53.52; H, 5.25.

2-Bromo-1,3,5(10)-estratriene-3,16α,17β-triol 16,17-diformate (3b): mp 187–188 °C (MeOH); yield 46%; IR (KBr) 3450 (OH), 1730 (C=O), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, s, 18-CH_3), 5.15 (1 H, d, J = 6 Hz, 17α-H), 5.32 (1 H, m, 16β-H), 6.73 (1 H, s, 4-H), 7.33 (1 H, s, 1-H), 8.03 and 8.13 (1 H, s, 16α- and 17β-OCOH). Anal. Calcd for $C_{20}H_{23}O_5Br$: C, 56.73; H, 5.43. Found: C, 56.77; H, 5.36.

4-Bromo-1,3,5(10)-estratriene-3,16α,17β-triol 16,17-diformate (3d): mp 222–224 °C (acetone); yield 42%; IR (KBr) 3450 (OH), 1730 (C=O), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, s, 18-CH_3), 5.15 (1 H, d, J = 6 Hz, 17α-H), 5.35 (1 H, m, 16β-H), 6.80 (1 H, d, J = 9 Hz, 2-H), 7.14 (1 H, d, J = 9 Hz, 1-H), 8.03 and 8.13 (1 H, s, 16α- and 17β-OCOH). Anal. Calcd for $C_{20}H_{23}O_5Br$: C, 56.73; H, 5.43. Found: C, 56.88; H, 5.62.

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A Retro-Diels–Alder Synthesis of 3-Pyrrolines

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In the course of our research in the design and synthesis of new antineoplastic agents, we required a method to prepare 1-methyl-3-pyrroline and related 3-pyrrolines. The reduction of pyrrole with zinc–acetic acid[1-3] or hydrochloric acid[4] gives 3-pyrroline contaminated with up to 35% of pyrrolidine.[5] A similar problem has been reported for the reduction of 1-methylpyrrole.[6] In addition to the mixture invariably obtained with this method, the scope is limited to simple 1- and 2-alkyl-3-pyrrolines.[7,8] We therefore undertook the development of a new synthesis of 3-pyrrolines.

The Diels–Alder Reaction has been used frequently as a method of protection for a double bond[9] or other functional group.[10-12] Modification can then be made on other functional groups, and the alkene can be regenerated in a thermal retro-Diels–Alder reaction. The synthesis of 1-methyl-3-pyrrole is given in Scheme I. Furan is pictured as the diene, but other dienes were also used and the results with several dienes are compared in Table I. The preparations of the Diels–Alder adducts and the subsequent reductions went cleanly. The final step, the retro-Diels–Alder reaction, proceeded in variable yield depending upon the diene used in the initial step and upon the thermolysis conditions.

Scheme I

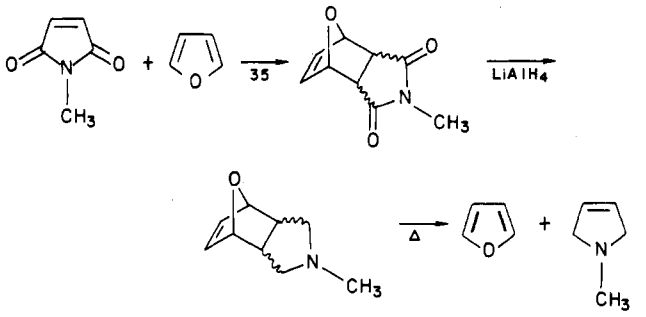

Table I. Synthesis of 1-Methyl-3-pyrroline

diene	% yield of Diels–Alder adduct	% yield of $LiAlH_4$ reduction	pyrolysis conditions temp., °C (method)[a]	pyrolysis % yield[b]
anthracene	93	83	500 (A)	*c*
furan	96	89	250 (A)	33
			300 (B)	0
			250–300 (C)	81[d]
cyclopentadiene	81	90	380–400 (C)	95[e]
dimethylanthracene	95	90	270	*f*

[a] Methods: A, adduct absorbed on sand and heated; B, adduct passed through a hot tube packed with glass beads; C, adduct dissolved in silicon oil and heated. [b] Yields were estimated by NMR. [c] The crude distillate contained a low yield of 1-methyl-3-pyrroline contaminated with an equivalent amount of 1-methylpyrrole. [d] Fractional distillation of the crude product gave pure 1-methyl-3-pyrroline in 60% isolated yield. [e] Fractional distillation of the crude product gave no pyrroline. [f] Pyrolysis not run on a preparative scale.

The best results were obtained when furan was used to prepare the adduct and the reduced adduct was pyrolyzed in a solution of silicon oil. The distillate from the reaction mixture consisted of a 1:1 mixture of furan and 1-methyl-3-pyrroline (60%). Thermolysis of the cyclopentadiene-protected material gave crude 1-methyl-3-pyrroline in ca. 95% yield, but attempts to purify 1-methyl-3-pyrroline by fractional distillation of the thermolysis product mixture led to extensive polymerization. No pyrroline was obtained. The adduct of 9,10-dimethylanthracene underwent thermolysis at a lower temperature than the adduct of anthracene. The high temperature required for the pyrolysis of the latter adduct resulted in the formation of a significant amount of *N*-methylpyrrole along with the desired 1-methyl-3-pyrroline.

The method was also used to synthesize *N*-phenyl-3-pyrroline. Thermolysis of the reduced adduct obtained from furan and *N*-phenylmaleimide gave the pure pyrroline in 83% yield. *N*-Phenyl-3-pyrroline had been previously synthesized in 35% yield from the reaction of aniline and *cis*-1,4-dichloro-2-butene.[14]

Functionalization of the α-position may be achieved by a Wittig reaction of the initial Diels–Alder adduct. The Wittig reaction of maleimide has been reported to give either mono- or disubstituted products depending on the condition employed.[15] Substitution at the β-position may

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