97.2, 61.1 (2 signals), 56.2 (2 signals), 50.5, 37.8, 30.5, 22.8. Minor conformer: ^{1}H NMR δ 7.63 (d, 1 H, C11, J = 8.8 Hz), 6.93 (d, 1 H, C10, J = 8.8 Hz), 6.65 (s, 1 H, C4), 5.56 (t, 1 H, C7), 5.13 (d, 1 H, NH), 3.96 (s, 3 H, 9-OCH_3), 3.93 (s, 3 H, 3-OCH_3), 3.90 (s, 3 H, 2-OCH_3), 3.53 (s, 3 H, 1-OCH_3), 2.70–2.05 (m, C5 and C6 protons from both conformers), 1.57 (s, 3 H, $COCH_3$); ^{13}C NMR δ 167.8, 161.0, 151.0, 144.1, 134.8, 126.9, 124.5, 114.5, 109.2, 61.3, 60.9, 39.7, 22.9. The remaining peaks are obscured by the peaks of the major conformer.

Biochemical Analyses. Pipes, EGTA, GTP (Type II-S), Sephadex G-50 were obtained from Sigma Chemical Co. Phosphocellulose (Whatman P11, Whatman Inc.) was precycled according to the manufacturer's instructions. [^{3}H]Colchicine was purchased from Dupont-New England Nuclear Research Products. Scintillation counting was performed on Beckman LS 7500. All experiments were done in PMEG buffer (0.1 M PIPES 1 mM $MgSO_4$, 2 mM EGTA, 0.1 mM GTP, pH 6.90 at 23 °C). If the ligand was not soluble in the buffer at the concentrations used, a small amount (<5%) of DMSO was included in the solutions.

Tubulin Purification. Tubulin was purified from bovine brain by two cycles of assembly/disassembly followed by phosphocellulose chromatography as previously described[11] and stored in liquid nitrogen. Prior to use, the frozen pellets were gently thawed, centrifuged at 5000g for 10 min at 4 °C and desalted into PMEG buffer on 1 mL Sephadex G-50 columns according to the method of Penefsky.[12] Tubulin concentrations were determined spectrophotometrically by the use of an extinction coefficient of 1.23 $(mg/mL)^{-1}$ at 278.5 nm in PMEG buffer.[13]

Inhibition of [^{3}H]Colchicine Binding to Tubulin. Solutions containing 50 μM of the ligand to be tested, 5 μM tubulin, and 5 μM [^{3}H]colchicine were incubated at 37 °C for 1.5 h. After incubation the ligand–protein complex was separated from unbound ligand by rapid gel filtration according to the method of Penefsky[12] as described previously.[13,14] The effluent was analyzed for [^{3}H]colchicine by scintilliation spectrometry. The percent inhibition of [^{3}H]colchicine binding was calculated relative to a control without added ligand. To indirectly assess the extent of covalent incorporation of compound 1 into tubulin, a sample containing compound 1 (50 μM) and tubulin (5 μM) was incubated for 45 min at 37 °C and then photolyzed at room temperature for a period of 20 min. (It was determined that 20 min was a sufficient amount of time to photolyze a 50 μM solution of 1.) A control was treated in the same manner. After photolysis [^{3}H]colchicine was added to achieve a final concentration of 5 μM, the sample was incubated for 1.5 h, and treated as described above.

Competitive Binding Assay. The ability of a ligand to competitively inhibit the binding of [^{3}H]colchicine was determined by a previously described procedure.[14,15] Tubulin (5 μM), the ligand to be tested (at concentrations of 0, 5, 10, 15, and 20 μM), and [^{3}H]colchicine (1, 2, and 4 μM) were incubated at 37 °C for 1.5 h. After incubation the ligand–protein complex was separated from unbound ligand by the method of Penefsky.[12] The effluent was then analyzed for [^{3}H]colchicine by scintillation spectrometry. The competitive inhibition constant (K_I) was determined by modified Lineweaver–Burke analysis of the data.[14,15]

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Registry No. 1, 129467-54-5; 2, 129467-55-6; 3, 129467-56-7; 4, 129467-57-8; 5, 129467-58-9; 6, 129467-59-0; 7, 129467-60-3; 8, 129467-61-4; 10-demethyl-10-tosylcolchicine, 129467-62-5; 9-demethyl-9-tosylisocolchicine, 129491-66-3; colchiceine, 477-27-0.

Supplementary Material Available: Original ^{1}H and ^{13}C NMR spectra of 10-demethoxy-10-tosylcolchicine, 9-demethoxy-9-tosylisocolchicine, and compounds 1–8 (18 pages). Ordering information is given on any current masthead page.

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Optically Active Amines. 35.[1] A Sector Rule for the Circular Dichroism of the Benzene Chromophore

Howard E. Smith* and Luca P. Fontana

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

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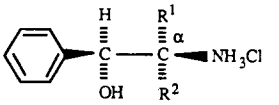
The circular dichroism (CD) of (αR)-norephedrine hydrochloride [($\alpha R,\beta S$)-**1a**] and (αS)-norpseudoephedrine hydrochloride [($\alpha S,\beta S$)-**1b**] both show a number of nega-



($\alpha R,\beta S$)-**1a**, $R^1 = CH_3$; $R^2 = H$

($\alpha S,\beta S$)-**1b**, $R^1 = H$; $R^2 = CH_3$

tive Cotton effects (CEs) from about 255 to 270 nm[2] associated with transitions from the lowest energy vibrational mode in the ground state to totally symmetric vibrational modes in the ^1L_b electronically excited state of the benzene chromophore,[2-4] the lowest energy CE being associated with the ^1L_b band origin. Occasionally, for other benzene compounds, additional, weak CD maxima are observed within the ^1L_b band with signs opposite to that of the ^1L_b band origin. These latter CD maxima are associated with transitions to nontotally symmetric vibrational modes in the electronically excited state.[4]

For benzene compounds without an additional substituent, vibronic borrowing from benzene transitions at shorter wavelength[5-8] gives the sign to the ^1L_b CEs, and the sign depends only on the chirality of the chiral center immediately attached to the benzene ring and is the same as that observed in the optical rotatory dispersion[9] (ORD) and CD spectra[10-13] of other phenylalkylcarbinols of the same generic configuration, also with a second chiral center contiguous to that attached to the benzene ring. The sign of the ^1L_b CEs for transitions to totally symmetric vibrational modes in the excited state can be predicted provided

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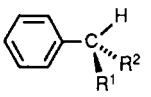
Table I. Circular Dichroism Data for Chiral Phenylcarbinamines, Phenylcarbinols, and Related Compounds[a]



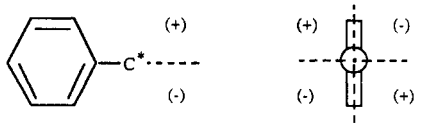
code	R^2	^1L_b band origin, λ_{max}, nm ($\Delta\epsilon^b$) (ref[c]): R^1 = CH_3 [(*R*)-**2**]	R^1 = CO_2H [(*S*)-**3**]	R^1 = CO_2^- [(*S*)-**4**]	R^1 = $C(CH_3)_3$ [(*R*)-**5**]
a	NH_2	268 (−0.11) (7)[d]			268 (−0.34) (8)[d,e]
b	NH_3Cl	267 (−0.082) (7)[d]	267 (−0.27) (14)[f]	268 (−0.23) (14)[g,h]	266 (−0.036) (8)[d,i]
c	OH	268 (−0.17) (15)	267 (−0.11) (14)[g]	260 (−0.11) (16)[d,j,k]	268 (−0.39) (17)[l,m]
d	OCH_3	268 (−0.075) (18)[d,n]	267 (−0.061) (19)[d]	261 (−0.17) (16)[d,j,k]	
e	$N(CH_3)_3I$	269 (−0.21) (20)[d,l]			269 (−0.24) (*o*)[d]
f	Cl	273 (−0.033) (*o*)[d]			
g	SH	270 (+0.27) (*o*)[d]			
h	CH_3		261 (+0.058) (16)[j,k,l]	261 (−0.089) (16)[j,k]	267 (−0.16) (21)[d,m,p]

[a] Methanol as solvent or as otherwise noted. [b] Molar dichroic absorption, $\Delta\epsilon = [\theta]/3300$ where $[\theta]$ is the molecular ellipticity. [c] Original report of complete electronic absorption (EA) and circular dichroism (CD) spectral data. [d] Enantiomer used. [e] Isooctane as solvent. [f] 0.1 N HCl as solvent. [g] Water as solvent. [h] No chloride ion present. [i] 1,1,1,3,3,3-Hexafluoropropanol as solvent. [j] Center maximum of three ^1L_b Cotton effects. [k] 0.15 N NaOH as solvent. [l] Ethanol as solvent. [m] Data from a figure. [n] 95% ethanol as solvent [o] This work. [p] Methylcyclohexane–isopentane (1:3) as solvent.

the preferred conformation of the chiral group about its attachment bond to the benzene ring is known, and an empirical sector rule allows the summation of the rotatory contribution of the groups attached to the chiral center. For the formulation of such a rule, we have used the CD data for the group of compounds in Table I.

Results and Discussion

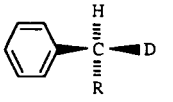
For substituted benzene compounds, empirical potential function and molecular orbital calculation[22-24] as well as X-ray,[23,25] proton nuclear magnetic resonance,[24,26-28] gas electron diffraction,[29] and jet laser spectroscopy[30] indicate that the preferred conformation is such that a hydrogen atom at the contiguous carbon center eclipses or almost eclipses the phenyl ring plane. Thus the compounds in Table I all have a preferred conformation somewhat similar to that shown at the top of Table I in which the hydrogen atom eclipses or has the greatest preference to eclipse the benzene ring plane. This conformational preference and the CD data in Table I suggest the quadrant projection I. In Table I, only the molar dichroic absorption ($\Delta\epsilon$) for the ^1L_b band origin is given, but complete electron absorption and CD data are reported elsewhere as is indicated in Table I.



near quadrants — all quadrants

Ia — Ib

The signs shown on projection I give the CD contribution to the ^1L_b CEs by groups lying in the four quadrants. The sum of these contributions gives the sign to the CEs of the ^1L_b band, and the signs for the quadrants follow from the observed negative CEs for (*R*)-1-phenylethanol [(*R*)-**2c**] and the assumption of a larger rotatory contribution for a methyl group as compared to that for an hydroxyl group. This latter assumption is based on a larger effective bond transition moment for a carbon–carbon bond as compared to that of a carbon–oxygen bond.[31] The sector signs in quadrant projection I are opposite to those suggested earlier by ORD observations.[32] These assignments were based on an incorrect assessment of the rotatory contribution of the methyl group[33] and were supported by an analysis of the CD spectra shown by a number of chiral α-deuteriophenylalkanes[34] [(*S*)-**6a–c** and (*R*)-**6d,e**], which all show positive ^1L_b CEs.[34]



(*S*)-**6a**, R = CH_3
b, R = CD_2H
c, R = $CH_2CH_2CH_3$
(*R*)-**6d**, R = CH_2OH
e, R = CH_2Br

Although the preferred conformation of (*S*)-**6a–c** and (*R*)-**6d,e** has the R–C bond perpendicular to the benzene ring plane (IIa),[24,26] other conformers of higher energy may be depicted as IIb and IIc. As a result of the smaller vibrational amplitude of the C–D bond, it was assumed[34] that there is a perference for the C–D bond to eclipse the benzene ring plane (IIb) rather than the C–H bond to eclipse this plane (IIc). Thus the R group in (*S*)-**6a-c** and (*R*)-**6d,e** is preferably in a near, lower or far, upper sector. Since the R group is the major contributor to the ^1L_b CEs, a positive sign for the ^1L_b CEs gives a positive sign to the

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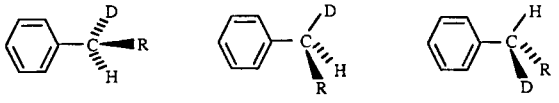
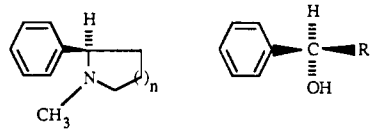
near, lower and far, upper sectors, opposite to those shown in quadrant projection I.



IIa IIb IIc

In agreement with IIb as preferred to IIc for (*S*)-**6a–c** and (*R*)-**6d,e**, CD measurements using deuterio-substituted cyclohexanones show that an axially oriented deuterium atom is energetically perferred over the corresponding equatorial one.[35,36] Recent work[37-39] with deuterio-substituted cyclohexenes and cyclohexanes, however, indicates that in some circumstances a deuterium atom is energetically more stable in an equatorial conformation than in an axial one. Similar circumstances may make IIc more stable than IIb, and positive ^1L_b CEs for (*S*)-**6a–c** and (*R*)-**6d,e** may be consistent with quadrant projection I.

Using the CD data in Table I, sequences for the summation of contributions to the ^1L_b CEs are SH, CO_2^-, $C(CH_3)_3 > CH_3 > NH_2$, $^+NH_3$, $^+N(CH_3)_3$, OH, OCH_3, Cl; and $CH_3 > CO_2H > {}^+NH_3$, OH, OCH_3. These sequences may be used in connection with the sector signs in quadrant projection I and will have a general usefulness for the establishment of the absolute configurations of related chiral benzene compounds in which one substituent at the contiguous chiral center is a hydrogen atom. Since a methyl group makes a larger contribution to the ^1L_b CEs than does an amino, ammonium, hydroxyl, or methoxyl group, any phenylalkylcarbinamine, carbinamine salt, or carbinol or their *N*-alkyl or *O*-alkyl derivatives with the same generic configuration as (*R*)-**2a–d** is predicted to show negative ^1L_b CEs. Included in this group are (*R*)-1-methyl-2-phenylpyrrolidine[40,41] [(*R*)-**7a**] and (*R*)-1-methyl-2-phenylpiperidine[41,42] [(*R*)-**7b**] which show negative ^1L_b CEs. In a phenylalkylcarbinol, the carbon atom



(*R*)-**7a**, n = 1
b, n = 2

(*S*)-**8a**, R = CH_2OH
b, R = CH_2Br
c, R = CF_3
d, R = $CH(CH_2OH)NHCOCHCl_2$-(*S*)

attached to the chiral center may have an hydroxyl, a halogen, or an amino substituent, and (*S*)-2-hydroxy-,[43] (*S*)-2-bromo- (see Experimental Section[41]), and (*S*)-2,2,2-trifluoro-1-phenylethanol[16,41] [(*S*)-**8a–c**], and (1*S*,2*S*)-2-(dichloroacetamide)-1-phenyl-1,3-propanediol[12] [(*S*)-**8d**] all show negative ^1L_b CEs.

Experimental Section

The melting point was taken in an open capillary tube and is corrected. The boiling points are also corrected. Rotatory powers at the sodium D line were measured with a Rudolph Research Autopol III automatic polarimeter and a 1-dm sample tube. Proton magnetic resonance spectra were observed using a JEOL FX-90Q spectrometer, and all compounds had spectra consistent with their assigned structures. Electronic absorption (EA) spectra were measured with a Cary Model 14 spectrometer with matched 1-cm cells and the normal variable slit. Circular dichroism (CD) spectra were obtained at 25–28 °C with a Cary Model 60 spectropolarimeter with a CD Model 6001 accessory. The sample cell was 1 cm, and the slit was programmed for a spectral band width of 1.5 nm. Cutoff was indicated when the dynode voltage reached 400 V. Spectral measurements began at 300 nm, and the molecular ellipticity ([θ]) values are adjusted to the maximum rotatory power previously reported or to an enantiomeric excess (ee) of 100%.

(*S*)-α-Phenylethyl chloride [(*S*)-2f] was formed by treatment of (*R*)-1-phenylethanol [(*R*)-**2c**], α^{25}_D +39.5° (neat), 86% ee,[44] in pyridine–pentane with phosphorus oxychloride, the reaction leading to inversion of the chiral center.[45] After distillation, (*S*)-**2f** had bp 70–72 °C (12 mmHg); α^{25}_D −94° (neat) [lit.[45] α^{20}_D +125.4° (neat, 1 dm) for the *R* isomer[46]]; EA_{max} (CH_3OH) 272 nm (ε 110), 269 (140), 265 (230), 258 (380), 253 (450), 246 (550), 216 (7300), 207 (8200); CD[47] (CH_3OH, *c* 0.0760) [θ]$_{281}$ ±0, [θ]$_{273}$ +110, [θ]$_{268}$ −40, [θ]$_{265}$ +120, [θ]$_{261}$ −99, [θ]$_{258}$ +49, [θ]$_{255}$ −79 [θ]$_{252}$ +59, [θ]$_{250}$ ±0; (*c* 0.00152) [θ]$_{250}$ ±0, [θ]$_{218}$ −8900, [θ]$_{215}$ −7800.

(*S*)-1-Phenylethanethiol [(*S*)-2g] was prepared from (*R*)-1-phenylethanol [(*R*)-**2c**], α^{25}_D +39.5° (neat), 86% ee,[44] by way of the Volante modification[48] of the triphenylphosphine dialkyl azodicarboxylate inversion procedure.[49] After purification of the thiol by way of its mercury(II) salt, (*S*)-**2g** had bp 82–84 °C (10 mmHg); $[\alpha]^{25}_D$ −87° (*c* 4.68, abs C_2H_5OH) [lit.[50] $[\alpha]^{25}_{589}$ +91.7° (*c* 6.17, abs C_2H_5OH) for the *R* isomer[46]]; EA_{max} (CH_3OH) 271 nm (ε 100) (sh), 265 (200), 262 (230), 259 (290), 256 (370); CD (CH_3OH, *c* 0.0330) [θ]$_{284}$ ±0, [θ]$_{270}$ −890, [θ]$_{267}$ −600, [θ]$_{264}$ −950, [θ]$_{259}$ −420, [θ]$_{256}$ −460, [θ]$_{253}$ −180 (sh), [θ]$_{245}$ ±0.

(*S*)-*N,N,N*-Trimethyl-α-phenylneopentylammonium iodide [(*S*)-5e] was prepared from (*S*)-α-phenylneopentylamine[51] [(*S*)-**5a**], $[\alpha]^{25}_D$ −5.4° (neat) [lit.[51] $[\alpha]^{21}_D$ +5.6° (neat, 1 dm) for the *R* isomer[46]], by first reductive (Eschweiler–Clarke) methylation with formaldehyde in aqueous formic acid and then reaction with methyl iodide. Thus (*S*)-**5e** had mp 180–185 °C; $[\alpha]^{25}_D$ −6.2° (*c* 1.16, CH_3OH); EA_{max} (CH_3OH) 269 mm (ε 280), 266 (190) (sh), 263 (370), 257 (330), 217 (22,000); CD (CH_3OH, *c* 0.100) [θ]$_{275}$ ±0, [θ]$_{269}$ +800, [θ]$_{266}$ +410, [θ]$_{263}$ +930, [θ]$_{260}$ +470, [θ]$_{257}$ +610, [θ]$_{253}$ +290 (sh), [θ]$_{240}$ ±0.

(*R*)-2-Bromo-1-phenylethanol [(*R*)-7b] was prepared by reduction of α-bromoacetophenone with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane,[52] prepared from 9-borabicyclo[3.3.1]nonane and (+)-α-pinene.[53] The reaction was allowed to proceed without solvent for 5 days at room temperature. Workup[53] and distillation gave (*R*)-**7b**: bp 79–80 °C (0.05 mmHg); $[\alpha]^{25}_D$ −33° (*c* 5.2, $CHCl_3$) [lit.[54] $[\alpha]^{25}_D$ −39° (*c* 8.00, $CHCl_3$), 93% ee]; EA_{max} (CH_3OH) 269 nm (ε 54) (sh), 266 (110) (sh), 263 (200), 260 (170) (sh), 257 (260),

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254 (190) (sh), 251 (230), 247 (200); CD (CH_3OH, c 0.112) $[\theta]_{274}$ ±0, $[\theta]_{268}$ +370, $[\theta]_{265}$ +180, $[\theta]_{262}$ +430, $[\theta]_{259}$ +290, $[\theta]_{256}$ +340, $[\theta]_{253}$ +240.

Registry No. (*S*)-**2a**, 2627-86-3; (*S*)-**2b**, 17279-30-0; (*R*)-**2c**, 1517-69-7; (*S*)-**2d**, 2511-06-0; (*S*)-**2e**, 17279-33-3; (*S*)-**2f**, 3756-41-0; (*S*)-**2g**, 33877-11-1; (*S*)-**3b**, 38329-34-9; (*R*)-**7b**, 80988-38-1; (*R*)-**3d**, 3966-32-3; (*S*)-**3h**, 7782-24-3; (*S*)-**4b**, 2935-35-5; (*R*)-**4c**, 54385-47-6; (*R*)-**4d**, 130409-50-6; (*S*)-**4h**, 130409-51-7; (*S*)-**5a**, 82729-98-4; (*S*)-**5b**, 108082-57-1; (*R*)-**5c**, 23439-91-0; (*S*)-**5e**, 130409-52-8; (*S*)-**5h**, 36238-13-8; (*S*)-**3c**, 17199-29-0.

Hypervalent Iodine Oxidation of *N*-Acyltyramines: Synthesis of Quinol Ethers, Spirohexadienones, and Hexahydroindol-6-ones

Yasuyuki Kita,* Hirofumi Tohma, Kazumi Kikuchi, Masanao Inagaki, and Takayuki Yakura

Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, 565 Osaka, Japan

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There is an increasing interest in the hypervalent iodine oxidation of phenols and related compounds. Although reaction of phenols themselves with phenyliodine(III) diacetate (PIDA) or phenyliodine(III) bis(trifluoroacetate) (PIFA) frequently leads to resinous products,[1,2] some para-substituted phenols (electron-withdrawing) yield *p*-benzoquinones.[2] Phenols bearing electron-withdrawing *o*-nitro and *o,p*-dinitro groups react with PIDA to give the corresponding iodonium salts[3] and some hindered phenols to give the corresponding quinol ethers.[4] Hypervalent iodine reagents have been also used for the oxidative cyclization of bisnaphthols to spiro compounds,[5] for intramolecular oxidative aryl–aryl coupling,[6] and for carbon–carbon bond cleavage of NH_2-tyrosine dipeptides.[7] As part of our continuing studies on hypervalent iodine chemistry,[8] we have reported the oxidation of para-substituted phenol derivatives leading to *p*-benzoquinone monoacetals,[9] spiro compounds,[9] *p*-benzoquinones,[10] and azacarbocyclic spiro dienones.[11] We have now examined the hypervalent iodine oxidation of *N*-acyltyramines **1a–d**, which have the amido group as the para substituent. Oxidation of **1** with PIFA leads to two modes of reaction, depending on the solvent used: (i) in a nucleophilic solvent such as alcohol or acetic acid, the solvent attacks the para position of **1** to give the corresponding quinol ether **2** and (ii) in a poorly nucleophilic polar solvent such as 2,2,2-trifluoroethanol,[12] cyclization occurs by the attack of the amido group to give the spirocyclohexadienone **3**.

A typical experimental procedure for the reaction of *N*-acetyltyramine (**1a**) with PIFA is as follows. To a solution of **1a** in anhydrous methanol was added 1.2 equiv of PIFA. The mixture was stirred at room temperature for 10 min to give **2a** in 76% yield. Oxidation of **1a** with PIFA in other nucleophilic solvents such as ethanol, 2-propanol, and acetic acid proceeded rapidly under similar conditions to give the corresponding quinol ethers **2b–d** as major products. Similarly, other phenols (**1b–d**) reacted with PIFA to give the corresponding quinol ethers **2e–j**. On the other hand, reaction of **1a–d** with PIFA in 2,2,2-trifluoroethanol or in methylene chloride in the presence of potassium carbonate gave mainly the spirocyclohexadienone derivatives **3a–d**, respectively.[13]

Next, we examined the PIFA oxidation of *N*-alkyl-*N*-benzoyltyramines. Treatment of *N*-methyl- and *N*-ethyl-*N*-benzoyltyramines **1e,f** with PIFA in 2,2,2-trifluoroethanol followed by aqueous workup gave the hexahydroindol-6-ones **4a,b** in fair yields. Similar results were observed in the thallium(III) trifluoroacetate (TTFA) oxidation of *N*-alkyl-*N*-benzoyltyramines.[14] An effort to convert the previously obtained spirocyclohexadienone **3c** to **4a,b** by alkylation followed by hydrolysis failed. The formation of **4a,b** by alkylation followed by hydrolysis failed. The formation of **4a,b** from **1e,f** can be explained by an intramolecular Michael-type addition of the amino group to the double bond of the dienone intermediate (**A**) (Scheme I). The reaction conditions, products, and yields are listed in Tables I and II.

The spiro dienone derivatives are not only useful synthetic intermediates but also a part of the structure of many pharmacologically important compounds,[15,16] and the hexahydroindolone is a useful intermediate in the synthesis of the lycorine alkaloids.[17]

Experimental Section

All melting points are uncorrected. IR absorption spectra were recorded in $CHCl_3$. ^1H NMR spectra were measured at 90 or 500 MHz with $CDCl_3$ as a solvent unless otherwise noted. Mass spectra were obtained with a direct inlet system. E. Merck silica gel 60 (70–230-mesh ASTM) for column chromatography and E. Merck precoated TLC plate, silica gel 60 F_{254}, for preparative thin-layer chromatography (preparative TLC) were used. The organic layers were dried with anhydrous $MgSO_4$. The known starting materials were prepared by reported methods: **1a**,[18] **1c**.[19] Other unknown *N*-acyltyramines **1b,d** were prepared by the

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