1 and 2 were used as a multiple probe to calculate the thermodynamic parameters of dimerization of each. Consequently, the energetics associated with intramolecular hydrogen bonding in these molecules could be derived with a high level of certainty. These findings are important for understanding and predicting preferred conformations of heterocyclic structures and in particular those of naturally occurring ionophores, such as nonactin, monensin, lasalocid, etc.,[10] and polyoxo macrolides, such as erythromycin, pikromycin, etc.[11] The conformations of such complex molecules have attracted the attention of chemists and biochemists in the past two decades, and also undoubtedly have an important bearing on structure-activity relationships of these antibiotics in biological systems.

Experimental Section

Samples of (+)-(*S,S*)-(*cis*-β-methyltetrahydropyran-2-yl)acetic acid (**1**) and (−)-(2*R*,6*S*)-(*trans*-β-methyltetrahydropyran-2-yl)-acetic acid (**2**) were prepared as reported.[4] NMR spectra were recorded on a Bruker AM-300 spectrometer operating at 300 MHz using 5-mm o.d. NMR tubes. Samples of **1** and **2** were prepared as solutions in analytical grade $CDCl_3$ and various concentrations (0.27, 0.18, 0.12, 0.06, 0.015, 0.0075, 0.0037, and 0.00093 M) were made up by serial dilution. NMR spectra were taken at four different temperatures: 313, 293, 273, 253 K. For each concentration, the spectrum at each of the four temperatures was obtained after waiting at least 15 min to allow for equilibration. At the higher concentration, only eight scans were taken, while for dilute samples more scans (up to 100) were required. Tetramethylsilane (Me_4Si) was used as an internal standard. The spectra were generated by using a spectral window of 2400 Hz, 16 384 data points, a pulse width of 75°, a recycle time of 3.5 s, and a line broadening of 0.2 Hz. The results were processed on the IBM-3081 at the Weizmann Institute of Science by using the PROC NLIN package of the Statistical Analysis System (SAS). The spectra shown in Figure 1 were recorded on a Bruker WH-270 spectrometer operating at 270 MHz.

Acknowledgment. We wish to thank the Israel National Council for Research and Development for their generous support. Dr. Hugo E. Gottlieb of Bar-Ilan University is acknowledged for providing access to their Bruker AM-300 spectrometer.

Registry No. 1, 69493-11-4; 2, 69493-16-9.

Supplementary Material Available: Van's Hoff plot for H-2 in compound 1 (1 page). Ordering information is given on any current masthead page.

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Intramolecular Hydrogen Bonding Enhances the Rate of Nucleophilic Cleavage in Alkyl–Aryl Ethers

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Cleavage of alkyl–aryl ethers in acid solution is generally accepted to require equilibrium protonation of the ether oxygen prior to nucleophilic displacement of phenol from the alkyl carbon atom by halide ion.[1] Such protonation serves to polarize the alkyl carbon–oxygen bond, making the carbon more susceptible to nucleophilic attack, and to convert phenoxide into a neutral phenol leaving group. A variety of mild and selective ether cleaving reagents, active in nonaqueous solvents, have been reported in which protonation has been replaced by the coordination of Lewis acids to the ether oxygen.[2] Increasing the nucleophilicity of the halide ion through phase-transfer catalysts,[3] in situ generation of HI in nonaqueous solvents,[4] or the use of high temperatures and poorly solvating solvents[5] also leads to ether cleavage by halide ions in the absence of aqueous acid.

We postulated that if the C–O activation requirement could be met by an intramolecular hydrogen bond to the basic ether oxygen atom, selective nucleophilic ether cleavage by halide ion could be effected at moderate temperatures in a basic solvent such as pyridine. The original motivation for the studies reported here was the observation that pyridine hydriodide (py–HI) or anhydrous lithium iodide in pyridine at 50 °C modified fractions of a bituminous coal in a manner consistent with ether cleavage.[6] However, we have previously shown that monofunctional ethers such as anisole, benzyl phenyl ether, and dioctyl ether are not cleaved by py–HI below 200 °C.[7] Since ortho, but not para, anisic acid was demethylated by py–HI in pyridine at 85–115 °C, we suggested that intramolecular hydrogen bonding activated the alkyl C–O bond toward nucleophilic attack by iodide ion.

Royer and co-workers have shown that molten pyridine hydrogen halide salts (py–HX) will dealkylate methoxy aromatics at elevated temperatures (190–230 °C) and that the rates of these reactions are retarded by the presence of free pyridine or quinoline.[8] We have also shown[7] that py–HI converts anisole, benzyl phenyl ether, phenyl phenethyl ether, and cyclohexyl phenyl ether to the phenol and hydrocarbon[9] when heated without solvent in evacuated, sealed tubes at 210 °C but that these and other monofunctional alkyl–aryl ethers are more than 90% recovered after 4 days in pyridine solutions containing excess HI at 115 °C. Anhydrous LiI in boiling collidine (174 °C) demethylates methoxy naphthalene[5a] and converts 1,2-dimethoxybenzene into 2-methoxyphenol but does not demethylate *p*-anisic acid.[5b] *p*-Anisic acid, 2-methoxyphenol, and 2-benzyloxyphenol are also recovered unchanged from pyridine solutions of py–HI or LiI after three days at 115 °C.[7]

In order to further test the hypothesis that intramo-

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0022-3263/86/1951-4291$01.50/0

Chart I

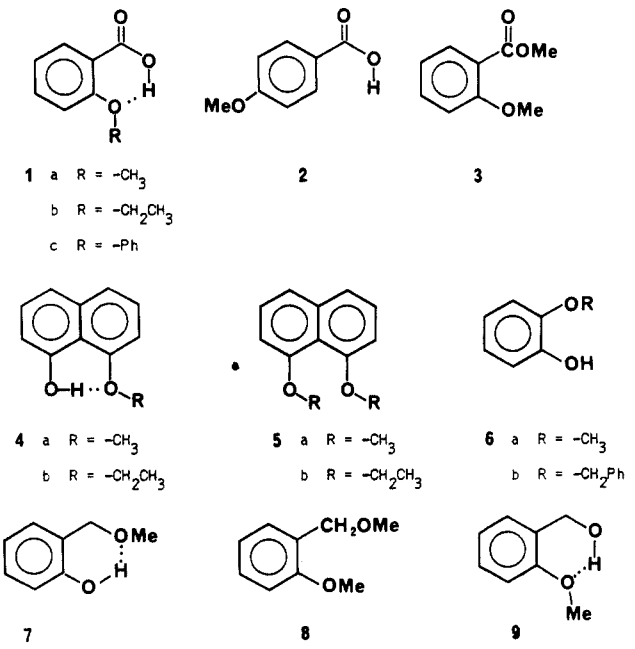


Table I. Observed (Pseudo) First-Order Dealkylation Rate Constants in Pyridine

ether	HI (115 °C) 10^6k, s^{-1}	LiI (115 °C) 10^6k, s^{-1}	MI	10^6k, s^{-1}	T, °C
		H-Bonded Ethers			
1a	45	31	$LiI{\cdot}3H_2O$	2.8	85
1a			KI	3.8	115
1b	4.3	*a*			
1c	*b*	*a*	$LiI{\cdot}3H_2O$	*b*	105
4a	3.5	9.8	LiI	0.2	50
4a			$LiI{\cdot}3H_2O$	2.6	105
4a			KI	0.5	115
4b	*b*	1.2			
7	6.7	83	LiI	0.2	50
9	7.0	*a*			
		Non-H-Bonded Ethers			
2	*b*	*b*			
3	0.5[c]	180[c]			
5a	*b*	0.9	LiI	*b*	50
5a			$LiI{\cdot}3H_2O$	0.5	105
5b	*b*	*b*			
6a,b	*b*	*b*			
8	0.2	*a*			

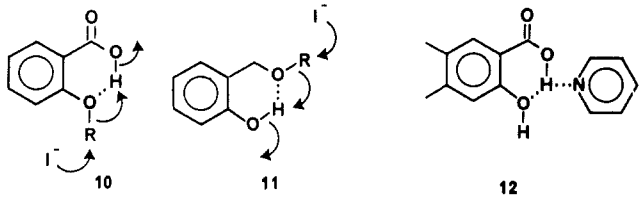
[a] Not determined. [b] No reaction products detected, >92% ether remaining. [c] Ester cleavage rate; ether does not react.

lecular hydrogen bonding can activate ethers toward nucleophilic cleavage, we studied the reactions of the alkyl–aryl ethers shown in Chart I with iodide salts in pyridine at 115 °C, conditions where monofunctional ethers do not react. Since the solvent is more basic than the ether and in much higher concentration, protonation of the ether by external agents should be relatively unimportant and the only source of C–O activation available is intramolecular hydrogen bonding. Reactions of those structurally similar compounds shown in Chart I which lack intramolecular H bonds served as controls.

We now report that enhancement of nucleophilic ether cleavage by py–HI and LiI in pyridine by intramolecular hydrogen bonding appears to be general for compounds in which an alkyl ether oxygen is the acceptor atom of an intramolecular hydrogen-bonded six-membered ring. Isomers or related compounds lacking the hydrogen bond are cleaved slowly or not at all under identical conditions. Anhydrous lithium iodide in pyridine cleaves ethyl- and methyl–aryl ethers containing such intramolecular hydrogen bonds at temperatures below 115 °C, a potentially useful method for the selective dealkylation of acid-sensitive compounds.

Results and Discussion

Dealkylation rate constants for 31 combinations of iodide salts and the ethers shown in Chart I are given in Table I. Compounds **1a**, **1b**, **4a**, **4b**, **7**, and **9**, which contain intramolecular hydrogen bonds as part of a six-membered ring, show enhanced rates of ether cleavage by iodide ion compared with compounds **2**, **3**, **5a**, **5b**, and **8** which lack the H bond. Diaryl ether **1c**, which cannot react via the S_N2 mechanism, is also unreactive as are **6a** and **6b**, in which the H bond is part of a five-membered ring. The products of these reactions are the substituted phenols and alkylpyridinium iodide salts. Under the conditions of these experiments added alkyl iodides are rapidly converted to the pyridinium salts. We believe these observations are best explained by an S_N2 mechanism in which the nucleofuge is the intramolecularly hydrogen-bonded phenolic oxygen atom (structures **10** and **11**).



We have previously shown that the cleavage of ethers by py–HI in pyridine is neither catalyzed nor retarded by free radical initiators, transition-metal salts, or small amounts of water or alcohols.[7] A variety of evidence supports the presence of intramolecular hydrogen bonds of the type shown in **10** and **11** in pyridine solutions of ortho-substituted phenols and acids. Because pyridine is less polar than water, pK_a values of acids and phenols are 7–14 pK units higher in pyridine than in water[10] and these weak acids are largely unionized in this basic solvent. Fluorescence measurements of 3-hydroxy-2-naphthoic acid/pyridine mixtures in toluene support the existence of hydrogen bonding of the type shown in **12**.[11] Intramolecular hydrogen bonding in compound **1a** is also demonstrated[12] by its lack of association in the concentration range of our experiments, conditions where benzoic and 2-methylbenzoic acids are largely dimeric. Thus, both the lack of reaction on the part of monofunctional and non-hydrogen-bonded ethers as well as the evidence cited for the presence of the interactions shown in **10–12** support a mechanism such as **10** or **11** for these reactions. Intermolecular hydrogen bonding is not expected to be important in these reactions since the acids and phenols are hydrogen-bonded to the much more concentrated pyridine solvent with enthalpies of 7–11 kcal/mol.[13]

The data available on the variation of rate constant with alkyl group, while limited, is consistent with a nucleophilic displacement. Ethyl ethers **1b**, **4b**, and **5b** all react slower than the corresponding methyl ethers **1a**, **4a**, and **5a**. As expected for this mechanism, phenyl ether **1c** does not react at all.

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Several experiments with **1a** and py–HI using acetonitrile or Me_2SO as solvent gave no evidence of cleavage. For the cleavage reactions, pyridine could be providing favorable solvation of the iodide salts or acting as a general base catalyst as shown in **12**. Attempts to examine the reaction of LiI with the lithium salt of **1a**, prepared by titration of **1a** with either LiOH or *n*-BuLi, failed because the salt was not soluble in pyridine under the reaction conditions.

The nucleophilic ether cleavage of *o*-anisic acid (**1a**) reported here complements the well-documented[14] nucleophilic ester cleavage of phenyl salicylates. In both cases, intramolecular hydrogen bonding accelerates the cleavage reactions. The rapid nucleophilic *ester* cleavage of compound **3** by LiI in pyridine compared with the very slow reaction with py–HI is noteworthy and may result from coordination of Li^+ by the carboxyl oxygens. In both reactions of **3** with iodide salts the acyl iodide is presumed to be the initial product. It may react with pyridine under the reaction conditions but is converted to **1a** when aliquots are quenched and prepared for HPLC analysis (see Experimental Section). The relative magnitude of the rate constants for reactions of ether **1a** and ester **3** with py–HI gives further evidence that the acid proton in **1a** is necessary for cleavage. Ester cleavage in **3** is slower than ether cleavage in **1a** even though the ether group is still present in **3**. HPLC analysis of hydrolyzed aliquots taken during the reaction of **3** show acid **1a** to be the product.

The source of the iodide ion has a small effect on the rate of ether cleavage. Except in the case of *o*-anisic acid, anhydrous LiI is the most reactive salt. Pyridine hydriodide and $LiI{\cdot}3H_2O$ show similar rates, and both are faster than KI. Since $LiI{\cdot}3H_2O$ remains less soluble than LiI throughout the course of these reactions, it is likely that the iodide ion remains associated with the water molecules in pyridine solution. Hydrogen iodide forms a hydrogen-bonded ion pair with pyridine in the concentration range of our experiments and the I···H–N bond is unaffected by changes in concentration.[13] Since both phenols and acids are also hydrogen bonded to pyridine under the conditions of our experiments,[13] ion pairing and specific solvation of the salts may combine to produce the observed variations in rate as a function of iodide source. Complexing the lithium ion of LiI with tetramethylethylenediamine (TMEDA) appeared to increase slightly the cleavage rate of **1a**, but quantitative data could not be obtained since TMEDA interfered with the analytical methods used for these reactions. LiI is the most soluble of the salts and is most convenient for preparative scale reactions.

The contrast between the cleavage behavior of ethers **4** and **6** illustrates the importance of ring size on intramolecular hydrogen bonds. Although the strength of a hydrogen bond varies little with the O–H···O angle (θ) for values of $150° < \theta < 180°$, the bond strength is very sensitive to small changes in the O–H···O bond distance.[15] The importance of proper geometry on H bond strength is also illustrated by the similar cleavage rates of **7** and **9**, which have very similar chelate rings, but quite different donor acidities (phenol vs. alcohol).

This demonstration that intramolecular hydrogen bonding activates alkyl–aryl ethers toward cleavage by iodide ion in pyridine, taken with spectroscopic evidence that ethers in bituminous coal are hydrogen bonded to phenols,[16] explains the reported reactions of coal fractions with py–HI and LiI in pyridine.[6] Extension of the studies reported here to coal systems beyond those reported previously[6,7] is currently under way in our laboratories.

Experimental Section

General Data. The pyridine used for cleavage reactions was distilled from BaO under an N_2 atmosphere immediately prior to use. Melting and boiling points are reported uncorrected. NMR spectra were recorded on a Varian T-60 spectrometer in either $CDCl_3$ or acetone-d_6 containing Me_4Si as the reference. IR spectra were recorded on Perkin-Elmer 337 or Nicolet 20DXB spectrometers and mass spectra on a Du Pont Model 21-490 spectrometer. HPLC analyses were performed on a Beckman Model 342 system using a 15-cm C_{18} reverse-phase column. Elemental analyses of new compounds were performed by Galbraith Laboratories, Knoxville, TN. Compounds, **1**, **2**, **3**, **6**, and **9** were commercial samples whose purity was verified by physical and spectroscopic means before use. Anhydrous LiI (Aldrich) and $LiI{\cdot}3H_2O$ (Alfa) were stored in a desiccator and used without further purification.

Preparation of 1,8-Naphthalenediol (13). The method of Erdmann[17] was used to convert 1,8-naphthalene sultone (Fluka) into **13**[19] in 50% yield (mp 139–140 °C (lit. 140 °C)). This diol is very sensitive to oxidation-induced polymerization; solutions containing the diol produced an intractable, black deposit within 1 h if not carefully protected from air.

1,8-Naphthalenediol ethers (4a, 4b, 5a, 5b) were synthesized from **13** by a phase-transfer alkylation modification of the previously reported syntheses of **4a** and **5a**.[18] Monoethers **4a**[19] and **4b**[20] were produced in 61% and 88% isolated yields when the alkyl iodide, diol **13**, and tetra-*n*-butylammonium bromide in a 1.1/1.0/0.2 ratio were stirred at 40 °C with 10% aqueous NaOH and CH_2Cl_2 for 24 h. Crude ethers were separated from the neutralized reaction mixture by CH_2Cl_2 extraction followed by drying, decolorizing with activated carbon, solvent removal, and dry column chromatography (silica gel, CCl_4). Compound **4a** was recrystallized from ethanol, and **4b** was purified by molecular distillation at 72 °C (0.2 torr). Diethers **5a**[19] and **5b**[20] were produced in the same manner when the alkyl iodide to diol ratios, and the reaction times were increased. Alkyl iodide, **13**, and $(n\text{-Bu})_4NBr$ in a 3.3/1.0/0.5 molar ratio were stirred with CH_2Cl_2 and 10% NaOH at 40 °C for 24 h at which time a second 3.3 equiv of alkyl iodide was added and reaction continued for an additional 21 h. The crude diethers were recrystallized from ethanol to give a 67% yield of **5a** and a 51% yield of **5b**.

2-(Methoxymethyl)phenol (7)[19] was prepared from 2-hydroxybenzyl alcohol by Oka's method.[21]

1-Methoxy-2-(methoxymethyl)benzene (8)[19,22] was prepared in 52% yield from 2-hydroxybenzyl alcohol by the method employed for **5a**.

Pyridine hydriodide (py–HI)[19,23] was prepared in 78% yield from HI gas and pyridine in anhydrous toluene.

Ether cleavage reactions were conducted in well-stirred, anhydrous pyridine under pseudo-first-order conditions, under an inert atmosphere in small round-bottom flasks, in an electrically heated oil bath. Reaction products were identified by isolation from preparative scale experiments and by spiking HPLC and NMR analysis mixtures with authentic samples. Initial ether concentrations were varied from 0.03 to 0.4 M. Solubility con-

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siderations usually restricted initial concentrations of iodide salts to no more than 6 times the initial ether concentration for the most concentrated ether solutions used in the kinetic runs. For preparative scale cleavage reactions no problems were encountered when the iodide salts were not completely soluble at the start of the reaction.

In the small scale reactions (2–8 mmol of ether) used to determine the kinetic rate constants, changes in the concentration of ethers and products with time were followed by analyzing aliquots by HPLC for compounds **1**, **2**, **3**, and **6** or by quantitative proton NMR in $CDCl_3$ using 1-methylnaphthalene as the internal standard for compounds **1a**, **4**, **5**, **7**, **8**, and **9**. HPLC is more accurate and precise but requires tedious sample preparation in order to separate the analytes from iodide salts and solvent pyridine prior to injection onto the column. Quantitative NMR is less precise but requires no sample preparation. Rate constants for **1a** determined by both methods agreed within experimental error. For the HPLC analyses, aliquots were quenched in aqueous H_2SO_4, extracted with 1,2-dichloroethane, dried, diluted with acetonitrile, and concentrated on a C_{18} Sep-Pak cartridge (Waters) prior to analysis on a C_{18} reverse-phase analytical column using an $CH_3CN/H_2O/HOAc$ (23/75/2) mobile phase. Pseudo-first-order rate constants (k, s^{-1}) were calculated from the slope of a least-squares fit of ln $[C/C_0]$ vs. time data taken through at least 4 half-lives. Rate constant values reported in the table are averages of two or three reactions.

Acknowledgment. We thank the Illinois Coal Development Board and the Faculty Research Council of Eastern Illinois University for financial support and Kenneth Osborne, Linda Warfel, and Milind Vaidya for laboratory assistance during various phases of this study.

Registry No. **1a**, 579-75-9; **1b**, 134-11-2; **1c**, 2243-42-7; **2**, 100-09-4; **3**, 606-45-1; **4a**, 3588-75-8; **4b**, 104422-22-2; **5a**, 10075-66-8; **5b**, 104422-23-3; **6a**, 90-05-1; **6b**, 6272-38-4; **7**, 5635-98-3; **8**, 21998-86-7; **9**, 612-16-8.

Supplementary Material Available: Analytical and spectroscopic data for compounds **4a,b**, **5a,b**, **7**, **8**, **13**, **14**, and py–HI (3 pages). Ordering information is given on any current masthead page.

Nickel Boride/Hydrazine Hydrate: Reduction of Aromatic and Aliphatic Nitro Compounds. Synthesis of 4-(Benzyloxy)indole and α-Alkyltryptamines

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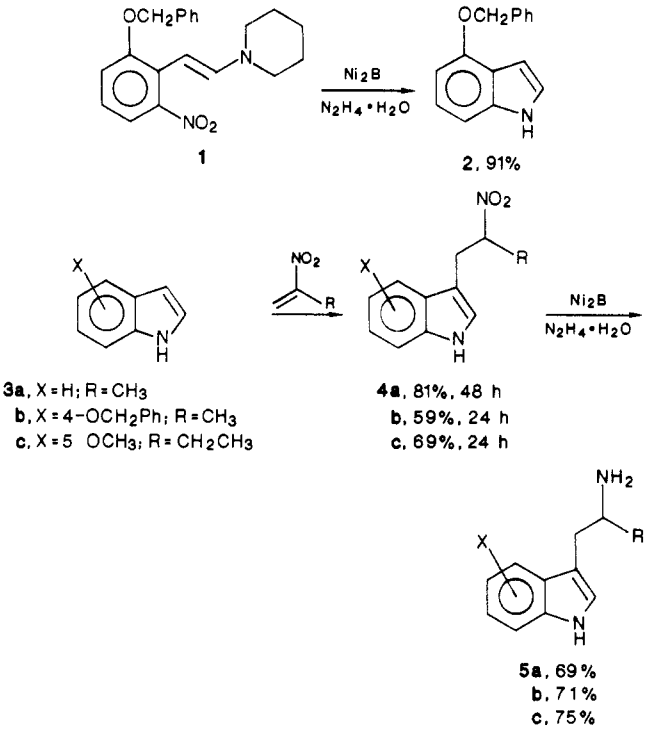
In the context of our ongoing research, it became necessary to prepare quantities of 4-, 5-, or 6-alkoxyindoles. We had developed a two-step synthesis from *o*-nitrotoluenes as a simplified variation of the Leimgruber and Batcho method.[1] For example, 2-(benzyloxy)-6-nitrotoluene was reacted with tripiperidinomethane (TPM) and the resulting nitropiperidinostyrene **1** was reduced with aqueous titanous chloride to provide 4-(benzyloxy)indole (**2**) in 65% overall yield.[2]

Although reductive cyclization proceeded rapidly and cleanly, a significant drawback of this method remained the somewhat tedious extraction of the indole from the aqueous reduction mixture, which contained titanium dioxide as a fine suspension. The tendency of this mixture to form emulsions decreased extraction efficiency and required the use of large solvent volumes for good product recovery.

A recent literature procedure[3] for the preparation of 4-(benzyloxy)indole uses Raney nickel and hydrazine hydrate to effect the reductive cyclization in high yield. We were curious to see if nickel boride (P-1 nickel) would also effect the reduction, as this catalyst is reported to be at least as active as Raney nickel in the hydrogenation of alkenes.[4] Obvious advantages over Raney nickel include its ease of preparation and nonpyrophoric nature.

Indeed, when an ethanolic solution of **1** in the presence of nickel boride was brought to reflux and several equivalents of hydrazine hydrate were added, gas was vigorously evolved and a rapid reductive cyclization occurred. After filtration, solvent removal, and flash chromatography,[5] 4-(benzyloxy)indole was obtained in 90% yield. In combination with the TPM condensation, this procedure may now be used easily to convert 2-(benzyloxy)-6-nitrotoluene to 4-(benzyloxy)indole in better than 80% overall yield with the use of inexpensive reagents and nonpyrophoric catalysts.



In a further investigation of the general utility of these reagents, we have discovered that similar reaction conditions also effect the reduction of aliphatic nitro compounds. Several substituted 1-(indol-3-yl)-2-nitroalkanes **4a–c** were reduced to the corresponding α-alkyltryptamines **5a–c** as illustrative examples. Indolylnitroalkanes were prepared by the condensation of substituted indoles **3a–c** with the appropriate nitroolefin, an extension of the method of Ranganathan.[6] It appears that a variety of substituted α-alkyltryptamines may be readily prepared by this two-step method.

Finally, it is interesting to note that while no use of nickel boride/hydrazine as a reduction system has been

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