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Superacidic Activation of Quinoline and Isoquinoline; Their Reactions with Cyclohexane and Benzene[1]

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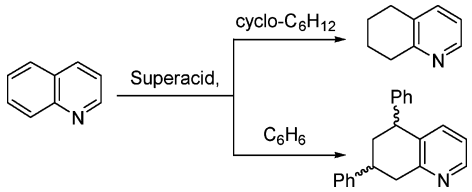
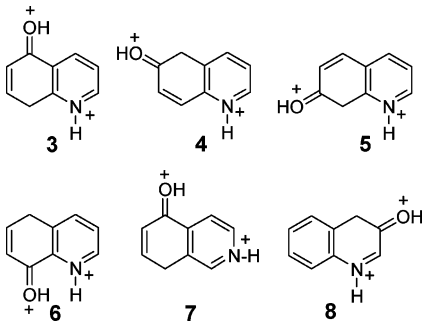
Received May 12, 2007



Quinoline (**1**) and isoquinoline (**2**), upon activation by strong acids, lead to intermediate N,C-diprotonated dications, which are involved in reactions with weak nucleophiles. Thus, **1** and **2** undergo selective ionic hydrogenation with cyclohexane in $CF_3SO_3H-SbF_5$, $HBr-AlBr_3-CH_2Br_2$, or $HCl-AlCl_3-CH_2Cl_2$ acid systems to give their 5,6,7,8-tetrahydro derivatives. They also readily condense with benzene in the presence of $HBr-AlBr_3$ or $HCl-AlCl_3$ to provide 5,6,7,8-tetrahydro-5,7-diphenylquinoline (**10**) and 5,6,7,8-tetrahydro-6,8-diphenylisoquinoline (**12**), respectively.

The facile N,C-diprotonation of quinoline (**1**) and isoquinoline (**2**) in strong acid solution was surmised based on the kinetic study of their H/D exchange reaction with deuteriosulfuric acid at high temperatures.[2] The deuteriation occurs at positions 8 > 5, 6 > 7 > 3 and 5 > 8 > 7 of **1** and **2**, respectively, indicating facile protonation of the carbocyclic ring of the N-protonated heterocycles.[2] Surprisingly, the literature appears to contain no reports on the use of this remarkable property of **1** and **2** as a method of electrophilic activation, which could be of interest from a synthetic point of view. Indeed, we recently have shown that a variety of isomeric hydroxy(iso)quinolines condense with benzene and undergo ionic hydrogenation with cyclohexane in protonic superacids or in the presence of excess of aluminum halides.[3] The key intermediates of these reactions were recognized to be superelectrophilic[4] N,C-diprotonated dications of the heterocycles. Moreover, many such long-lived dications **3**−**8** have been generated in the $CF_3SO_3H-SbF_5$ acid system.[3] Obviously, the hydroxyl group plays an important role in stabilizing these dicationic intermediates.



Taking into account practical importance of quinoline and isoquinoline scaffolds in organic chemistry, the objective of the present work is to extend our investigation to readily available parent compounds **1** and **2** and involve them in similar model reactions with cyclohexane and benzene in strong acids. The main aim of the work was also to generate nonstabilized N,C-diprotonated dications derived from **1** and **2** under the reaction conditions.

NMR Study of Protonation of 1 and 2 and a Theoretical Study of Probable N,C-Diprotonated Dications. Initially, we examined the protonation of **1** and **2** using such superacidic system as $CF_3SO_3H-SbF_5$ at 25 °C and more acidic HSO_3F-SbF_5(1:1)-SO_2ClF and $HF-SbF_5$(5:1)-SO_2ClF systems at −60 °C by means of ^1H and ^{13}C NMR spectroscopy. Unfortunately, under these conditions, only the N-protonated monocations of the precursors were formed as long-lived species, indicating, as expected, the difficulty of subsequent C-protonation. However, N,C-diprotonated species may be involved in a relatively small equilibrium.

The second protonation can lead to a number of isomeric N,C-diprotonated dications of structures **1a**−**e** and **2a**−**e**, respectively, as the most plausible (Table 1). In order to estimate the relative stabilities, electrophilicities, and positions of electrophilic centers of the preferred dications, we have calculated their relative energies, the energies of lowest unoccupied molecular orbital (ϵ_{LUMO}), the squares of the coefficients of carbon atoms at LUMO of electrophilic centers ($c_\bullet^2$) and the atomic charges of electrophilic centers ($q_\bullet$) localized at carbon atoms and pendent hydrogen atoms. Calculations were carried out with the Gaussian 98 program system.[5] The geometry optimization was performed using the DFT[6] method at the B3LYP[7]/6-31G* level.[8] Vibrational frequency at the B3LYP/

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(1) Chemistry in Superacids. Part 68. For part 67, see: Koltunov, K. Yu.; Prakash, G. K. S.; Rasul, G.; Olah, G. A. *Eur. J. Org. Chem.* **2006**, 4861.

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(3) (a) Koltunov, K. Yu.; Prakash, G. K. S.; Rasul, G.; Olah, G. A. *Heterocycles* **2004**, *62*, 757. (b) Koltunov, K. Yu.; Prakash, G. K. S.; Rasul, G.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 4330. (c) Koltunov, K. Yu.; Prakash, G. K. S.; Rasul, G.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 8943. (d) Koltunov, K. Yu.; Repinskaya, I. B. *Russ. J. Org. Chem.* **2002**, *38*, 437.

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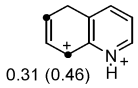
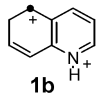
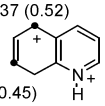
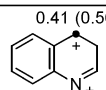
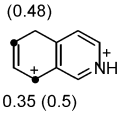
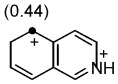
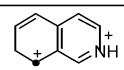
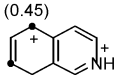
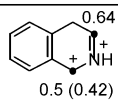
10.1021/jo070875x CCC: $37.00
Published on Web 08/18/2007

TABLE 1. Energies of the LUMO (ϵ_{LUMO}), the Square of the Coefficients on Carbon Atoms at the LUMO (c_i^2),[a] NBO Charges on CH Groups (q_i)[a] and Total Energies (−au), ZPE, and Relative Energies of Dications 1a−e and 2a−e Calculated by the DFT Method

dication, q• and ($c•^2$)	ϵ_{LUMO}, eV	B3LYP/6-31G*//B3LYP/6-31G*	ZPE	relative energy, kcal/mol
0.41 (0.41)  0.31 (0.46) **1a**	-13.002	402.46606	98.2	3.9
0.42 (0.53)  **1b**	-12.850	402.69571	100.7	6.0
 0.34 (0.41) **1c**	-13.077	402.45459	97.8	10.6
0.37 (0.52)  0.40 (0.45) **1d**	-12.839	402.46805	98.5	3.0
0.41 (0.56)  **1e**	-12.799	402.45328	98.3	12.1
0.41 (0.48)  0.35 (0.5) **2a**	-12.696	402.47280	98.5	0.0
0.43 (0.44)  **2b**	-13.151	402.45256	97.7	11.9
 0.43 (0.56) **2c**	-12.786	402.46108	98.0	6.9
0.35 (0.45)  0.43 (0.44) **2d**	-12.921	402.46802	98.4	2.9
0.64 (0.44)  0.5 (0.42) **2e**	-13.170	402.44677	98.2	16.0

[a] These parameters are given for atoms belonging to C-protonated ring and with the most significant values of c_i^2 at LUMO and q_i.

6-31G*//B3LYP/6-31G* level was used to characterize stationary point as minimum (number of imaginary frequency (NIMAG) = 0) and to evaluate zero point vibrational energies (ZPE), which were scaled by a factor of 0.98. Relative energies were calculated at the B3LYP/6-31G*//B3LYP/6-31G*+ZPE level. The values of $q•$ were obtained using natural bond orbital analysis[9] (NBO) method. Results of calculations are summarized in the Table 1.

All dications **1a**−**e** and **2a**−**e** according to the calculated values of the ϵ_{LUMO}s (∼−13 eV) are stronger electrophiles than their hydroxyl-substituted derivatives ($\epsilon_{LUMO} \sim -12.5$ eV)[3] and therefore appear to be capable of reacting with benzene and cyclohexane.

The computed relative energies show the order of favorable formation of the dications as follows, **1d** > **1a** > **1b** > **1c** > **1e** and **2a** > **2d** > **2c** > **2b** > **2e**, corresponding to second protonation of **1** and **2** in positions 8, 5, 6, 7, 3 and 5, 8, 7, 6, 4, respectively. This is in accordance with the previous deuteriation studies of **1** and **2** in D_2SO_4.[2]

Dication **2a** is more stable than dication **1d**, indicating that, in general, isoquinoline **2** is more easily activated (by N,C-diprotonation) than quinoline **1**. The significant values of both of $c•^2$ and $q•$ predict electrophilic reaction centers to be C^5 or C^7 and C^6 or C^8 for dications **1d** and **2a**, respectively. Similarly, one can easily predict electrophilic centers for other isomeric dications.

Reactions with Cyclohexane and Benzene. Compounds **1** and **2** did not react with benzene and cyclohexane in trifluoromethanesulfonic acid (CF_3SO_3H, $H_o = -14.1$) or in the presence of excess of aluminum halides at 20−100 °C. However, successful results were achieved in strong conjugate protic acid systems such as $CF_3SO_3H-SbF_5$ ($H_o \sim -18$), HBr−$AlBr_3$ ($H_o \sim -17.5$) or HCl−$AlCl_3$.

Quinoline **1**, for example, slowly reacts with cyclohexane in $CF_3SO_3H-SbF_5$ system at room temperature and in HBr−$AlBr_3-CH_2Br_2$ system at 70 °C over period of 24 and 150 h, respectively, to give 5,6,7,8-tetrahydroquinoline (**9**) as a single product (Scheme 1). According to the Scheme 1, the probable mechanism of this reaction includes generation of the dication **1d′** (as the major intermediate) followed by its selective ionic hydrogenation with cyclohexane.

More readily, over period 10 h at 25 °C, compound **1** reacts with benzene and with HBr−$AlBr_3$ to give 5,6,7,8-tetrahydro-5,7-diphenylquinoline (**10**) in 75% isolated yield (Scheme 1). The same reaction also takes place under the influence of HCl−$AlCl_3$, but more slowly—the conversion of **1** is about 40% over a period of 100 h at 25 °C. The preferred mechanism of the reaction, involving the intermediacy of the dication **1d′** and its subsequent condensation with benzene, is shown in Scheme 1.

Compound **2**, which according to theory (vide supra) is more easily activated than **1**, appears to be more reactive. Reaction of **2** with cyclohexane occurred in the $CF_3SO_3H-SbF_5$ system

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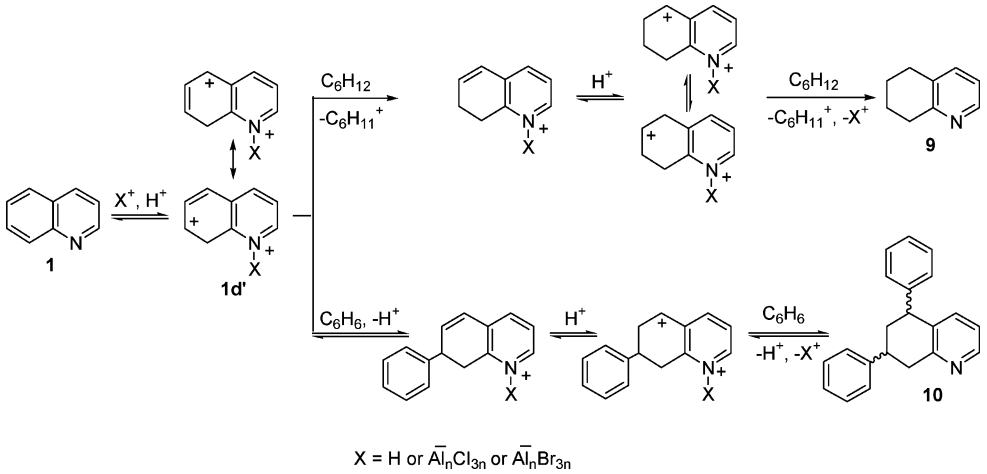
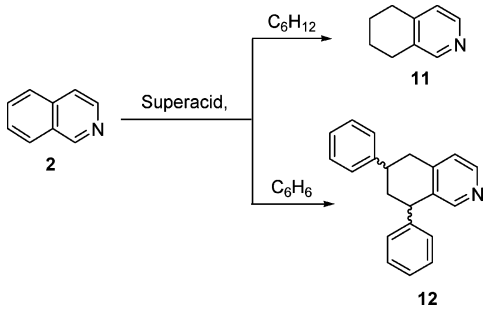
(8) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986.

(9) Reed, A. E.; Curtiss, L. A.; Wienhold, F. *Chem. Rev.* **1988**, *88*, 899.

SCHEME 1



SCHEME 2



at room temperature to give 5,6,7,8-tetrahydroisoquinoline (**11**) in 94% yield over a period of 2 h (Scheme 2). The reaction also took place slowly (period of half of the reaction ≥250 h) in HBr−$AlBr_3$−CH_2Br_2 and HCl−$AlCl_3$−CH_2Cl_2 acid systems at room temperature and in the presence of HCl−$AlCl_3$ at elevated temperatures (80−110 °C, in a pressure tube). Reacton of **2** with benzene occurred in the presence of HBr−$AlBr_3$ and HCl−$AlCl_3$ at room temperature to provide 5,6,7,8-tetrahydro-6,8-diphenylisoquinoline (**12**) in good yield (∼90%) over periods of 1 and 72 h, respectively (Scheme 2). The mechanism of the reactions of compound **2** with cyclohexane and benzene, which include the intermediacy of dication **2a** (or analogous protonated complexes with aluminum halides), is considered similar to that described in Scheme 1.

It should be stressed that the experimentally found regioselectivity of the reactions both of **1** and **2** with benzene corresponds to the involvement of the most stable (easily produced) dications **1d** and **2a**, respectively. This is not surprising, taking into account difficulty of the second protonation, which is regarded as a limiting step.

It should be also noted that both diphenyl-derivatives **10** and **12** are obtained mainly in the form of thermodynamically preferred *cis*-isomers. This was confirmed by X-ray crystallographic analyses performed on the hydrochloric acid salts of the predominant *cis*-**10** and minor *trans*-**12** isomers (Figure 1; see the Supporting Information for details).

Conclusions

In summary, compounds **1** and **2** undergo selective ionic hydrogenation with cyclohexane and condense with benzene in strong acidic media to give respective products **9**−**12**. All

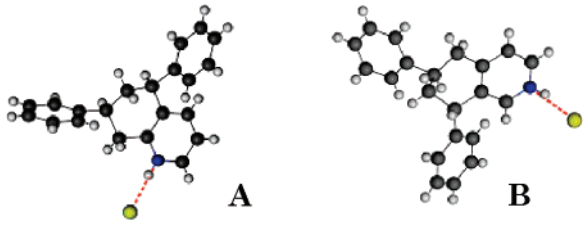


FIGURE 1. Molecular structure of *cis*-**10** (A) and *trans*-**12** (B) hydrochlorides.

experimental results can be successfully explained by the involvement of N,C-diprotonated dications of **1** and **2** as key superelectrophilic intermediates. This also conforms to results of theoretical calculations on these dications. In general, the observed reactivity of such nonactivated heterocycles as **1** and **2** seems promising for practical applications. We suggest that analogous approach can be followed to perform similar modifications of a large variety of aromatic heterocycles.

Experimental Section

5,6,7,8-Tetrahydroquinoline (9). Method a. To a solution of **1** (0.03 g, 0.23 mmol) in CF_3SO_3H (0.7 g, 4.7 mmol) was added SbF_5 (0.66 g, 3 mmol) at room temperature. After subsequent addition of cyclohexane (0.3 mL), the reaction mixture was stirred at 25 °C for 24 h. After the reaction, the reaction mixture was quenched with several grams of ice. The aqueous layer was washed with ether and then made basic with aqueous NaOH and extracted with ether. The organic phase was dried over anhydrous $MgSO_4$. Careful removal of the solvent under reduced pressure provided the mixture of product **9** and precursor **1** (0.029 g, the ratio 1:1). The mixture was separated by silica gel column chromatography with acetone−benzene as eluent to give product **9** (0.013 g, 42%) as a colorless liquid. NMR ^1H and ^{13}C data of **9** are comparable to those previously reported.[3b]

Method b. To a solution of $AlBr_3$ (2 g, 7.5 mmol) in CH_2Br_2 (2 mL) was added **1** (0.3 g, 2.3 mmol) and cyclohexane (2 mL). The resulting mixture was saturated with gaseous HBr (0.2 g, 2.5 mmol) and stirred at 70 °C in a 15 mL pressure tube for 150 h followed by workup described above to provide 0.28 g of the mixture of product **9** and precursor **1** (in a 1:1 ratio).

5,6,7,8-Tetrahydro-5,7-diphenylquinoline (10). To a solution of $AlBr_3$ (4 g, 15 mmol) in benzene (15 mL) was added **1** (0.6 g,

4.7 mmol). The resulting solution was saturated with gaseous HBr[10] (∼0.5 g, 6 mmol) and stirred at 25 °C for 10 h, then poured over ice. The resulting mixture was made basic with aqueous NaOH and extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to obtain the crude product,[11] which was purified by silica gel column chromatography with CH_2Cl_2 to give colorless syrup-like product **10** (1 g, 75%) as a mixture of cis/trans isomers (in a 3:1 ratio, respectively): HRMS $C_{21}H_{19}N$ calcd 285.1518, found 285.1509. Recrystallization from H_2O−ethanol (1:2) (provided with cooling at −20 °C) gave *cis*-**10** (0.57 g, 43%) as white crystals: mp 117−118 °C; ^{1}H NMR ($CDCl_3$) δ 2.12 (q, *J* 12 Hz, 1H), 2.37−2.43 (m, 1H), 3.2−3.4 (m, 3H), 4.25 (dd, *J* 12, 5.6 Hz, 1H), 7.01 (dd, *J* 7.8, 4.5 Hz, 1H), 7.1−7.4 (m, 11H), 8.41 (d, *J* 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 40.6 (C^7), 40.9 (C^6), 41.1 (C^8), 46.8 (C^5), 121.2 (C^3), 126.4, 126.5, 126.6, 128.5, 128.5, 128.6 (5-and 7-Ph, $C^{2'-6'}$), 134.8 (C^{10}), 137.1 (C^4), 145.1 (7-Ph, $C^{1'}$), 145.3 (5-Ph, $C^{1'}$), 147.2 (C^2), 156.9 (C^9).[12]

trans-**10**:[13] ^{1}H NMR ($CDCl_3$) δ 2.2−2.3 (m, 1H), 2.35−2.45 (m, 1H), 3.1−3.42 (m, 3H), 4.29 (t, *J* 4.9 Hz, 1H), 7.0−7.2 7.1−7.4 (m, 12H), 8.49 (dd *J* 4.7, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.9, 38.5, 39.6, 43.4, 121.4, 126.3, 126.3, 126.9, 128.3, 128.5, 128.7, 136, 138.1, 145, 146.1, 147.8, 157.3.

5,6,7,8-Tetrahydroisoquinoline (11). Method a. To a solution of **2** (0.04 g, 0.31 mmol) in CF_3SO_3H (1 g, 6.7 mmol) was added SbF_5 (0.8 g, 3.7 mmol). After subsequent addition of cyclohexane (0.2 mL), the reaction mixture was stirred at 25 °C 2 h followed by usual workup to give product **11** (0.039 g, 94%) as a colorless liquid. NMR data of **11** are comparable to those previously reported.[3b]

Method b. To a solution of $AlBr_3$ (2 g, 7.5 mmol) in CH_2Br_2 (2 mL) was added **2** (0.3 g, 2.3 mmol) and cyclohexane (2 mL). The resulting mixture was saturated with gaseous HBr (0.2 g, 2.5 mmol) and stirred at 25 °C for 250 h followed by usual workup to give 0.29 g as a mixture of product **11** and precursor **2** (in a 1:1 ratio).

5,6,7,8-Tetrahydro-6,8-diphenylisoquinoline (12). Method a. To a solution of $AlBr_3$ (4 g, 15 mmol) in benzene (15 mL) was added **2** (0.6 g, 4.7 mmol). The resulting solution was saturated with gaseous HBr[10] (∼0.5 g, 6 mmol) and stirred at 25 °C for 1 h, and after workup and purification described above for product **10** gave colorless syrup-like product **12** (1.21 g, 91%) as a mixture of cis/trans isomers (ratio 2.5:1, respectively): HRMS $C_{21}H_{19}N$ calcd 285.1518, found 285.1512.

cis-**12**:[13] ^{1}H NMR ($CDCl_3$) δ 2.09 (q, *J* 12.5 Hz, 1H), 2.42 (dd, *J* 12.5, 6.8 Hz, 1H), 3.1−3.24 (m, 3H), 4.26 (dd, *J* 12.5, 6.8 Hz, 1H), 7.0−7.4 (m, 11H), 8.09 (s, 1H), 8.33 (d, *J* 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 38.1, 40.7, 41.4, 45.7, 123.4, 126.6, 126.6, 126.7, 127.6, 128.5, 128.6, 128.8, 145, 145.9, 146.4, 146.6, 151.2.

trans-**12**:[13] ^{1}H NMR ($CDCl_3$) δ 2.2−2.3 (m, 1H), 2.35−2.45 (m, 1H), 2.8−3.3 (m, 3H), 4.39 (d, *J* 5 Hz, 1H), 7.0−7.4 (m, 11H), 8.25 (s, 1H), 8.38 (d, *J* 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.5, 36.8, 38.6, 41.8, 123.6, 126.3, 126.4, 126.8, 127.4, 128.3, 128.5, 128.6, 145.2, 145.8, 146.8, 146.9, 152.

Method b. To a stirred suspension of $AlCl_3$ (5.6 g, 42 mmol) in benzene (15 mL) was added **2** (2 g, 16 mmol). The resulting mixture was saturated with gaseous HCl and then maintained under stirring at 25 °C for 72 h. Workup and purification as described above gave **12** (3.71 g, 84%).

Acknowledgment. Support of this work by the National Science Foundation and the Loker Hydrocarbon Research Institute is gratefully acknowledged. We also thank N.V. Kuratieva and Dr. S.A. Gromilov (Nikolaev Institute of Inorganic Chemistry, Novosibirsk) for the X-ray analysis.

Supporting Information Available: Cartesian coordinates and total energies (hartrees) of the optimized geometries of **1a**−**e** and **2a**−**e**, ^{1}H and ^{13}C NMR spectroscopic data of **10** and **12**, and X-ray crystallographic data (CIF) for *cis*-**10** and *trans*-**12** hydrochloride salts. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070875X

(10) Gaseous HBr can be easily obtained by reaction of benzene with Br_2 in the presence of $AlBr_3$ and used without subsequent purification. Moreover, HBr can be produced in a "one pot reaction" by careful addition of Br_2 to the stirring solution of $AlBr_3$ and **1** (or **2**) in benzene at 0 to 5 °C.

(11) According to NMR and GC−MS data, the crude product contains **10** (>75%) along with variety of phenylquinolines, phenyltetrahydroquinolines, and unidentified 5,6,7,8-tetrahydrodiphenylquinoline (structural isomer of **10**, <10%). Crystallization of this mixture from aqueous ethanol gives *cis*-**10**.

(12) The structural assignment was performed by the INADEQUATE (^{13}C−^{13}C correlation) experiment on a 500 MHz NMR spectrometer (see the Supporting Information).

(13) The chemical shifts are taken from the spectrum of a mixture of the cis and trans isomers. The assignment of signals to each of these isomers was simplified by changing the ratio of the isomers using additional column chromatography treatments and other methods.