# Observable Magnetic Nonequivalence of Diastereotopic Protons as a Stereochemical Probe

David A. Walsh* and Edward E. Smissman†

*Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66045*

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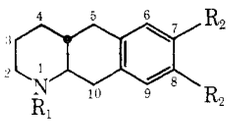
The *N*-benzyl derivatives of *cis*-decahydroquinoline, *trans*-decahydroquinoline, and *trans*-octahydrobenzo[*g*]quinoline were prepared in order to determine the stereochemistry of the ring juncture. The diasterotopic benzylic protons for the cis stereochemistry appear as an AB quartet in the nmr spectrum with a chemical shift difference of ~24 Hz, while the benzylic protons for the trans stereochemistry appear as an AB quartet with a chemical shift difference of ~60 Hz.

As part of the continuing work[1] in our laboratories on the synthesis of rigid analogs of biologically active phenethylamines, a series of *trans*-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolines (**1**) were prepared. Michne and Albertson[2] have reported on the synthesis of both *cis*- and



**1a.** $R_1 = H$; $R_2 = H$
**b.** $R_1 = H$; $R_2 = OCH_3$
**c.** $R_1 = COPh$; $R_2 = H$
**d.** $R_1 = COPh$; $R_2 = OCH_3$
**e.** $R_1 = CH_2Ph$; $R_2 = H$
**f.** $R_1 = CH_2Ph$; $R_2 = OCH_3$

*trans*-octahydrobenzo[*g*]quinoline ring systems. Decarboxylation of **2** gave **3** as a mixture of isomers. Conversion of **4** to **5** with 1:5 $H_2SO_4$:AcOH led to a mixture of approximately 60% *cis*- and 40% *trans*-**5**.[2b] The mixture could be separated by dry column chromatography, and the relative stereochemistry was assigned to each isomer by indirect chemical and spectral evidence.[2a]

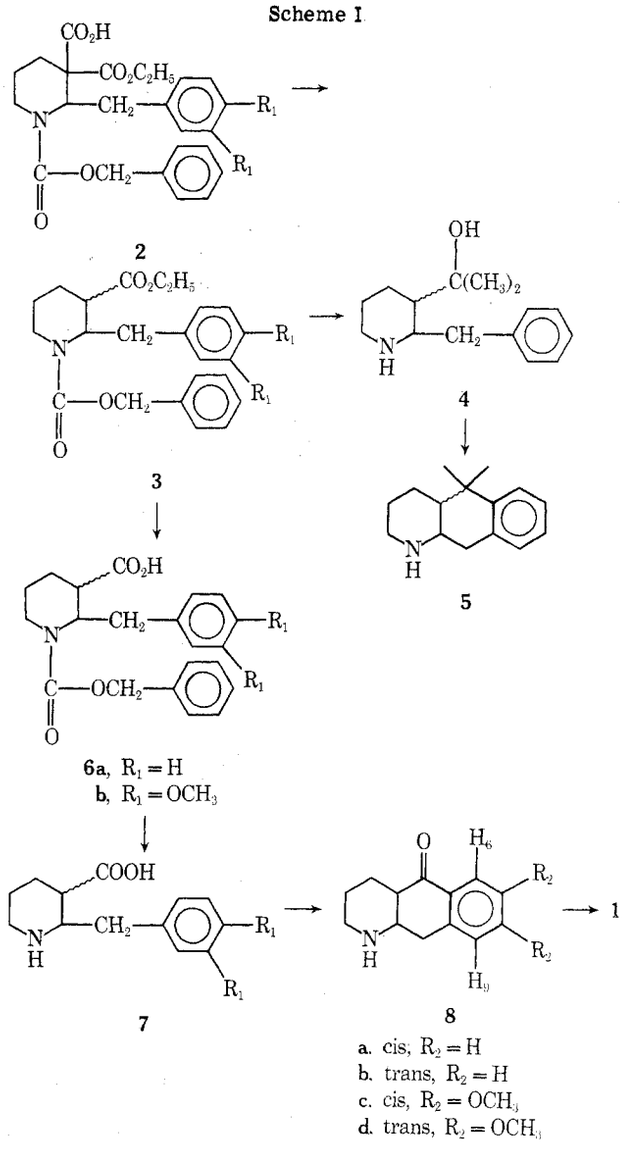
We wished to develop a synthetic procedure which would give only the trans stereochemistry for **1**, and we wanted an unequivocal method for determining this stereochemistry.

## Results and Discussion

The synthetic procedure[3] we chose utilizes **3** as starting material and is outlined in Scheme I. Hydrolysis of esters **3a** and **3b** followed by hydrogenation of **6a** and **6b** gave the desired amino acids, **7a** and **7b**, as a mixture of cis and trans isomers. Intramolecular cyclization of **7b** with 95% $H_2SO_4$ gave a ketone whose nmr spectrum showed three singlets for the aromatic protons in a ratio of 1($\delta$ 7.40):1($\delta$ 7.36):2($\delta$ 6.57). Proton $H_6$ is in a peri position to the benzylic carbonyl and is deshielded. The nmr resonance for $H_6$ should lie downfield with relation to that of $H_9$. The observation that there are two signals of equal intensity lying downfield from the $H_9$ singlet strongly suggests that sulfuric acid cyclization gives both **8c** and **8d** as products, analogous to the example of Michne and Albertson.[2] However, cyclization of **7b** with polyphosphoric acid (PPA) gave a ketone whose nmr spectrum showed only two singlets for the aromatic protons in a ratio of 1($\delta$ 7.36):1($\delta$ 6.57). Since the PPA cyclization appeared to give only one isomer, the question of the stereochemistry of this product was approached.

Lyle[4] and coworkers have determined the conformational requirements for observable magnetic nonequivalence of benzylic methylene protons in 2- and 3-alkyl-*N*-benzylpiperidines. The diastereotopic benzylic protons appear as an AB quartet in the nmr spectrum if a 2-alkyl substituent is equatorial and appear as a singlet if the 2-alkyl substituent is axial. In the 3-alkyl series, the benzylic protons appear as an AB quartet if the 3-alkyl substituent is either axially oriented or is a branched chain and equatorial. The octahydrobenzo[*g*]quinoline system can be considered as a 2,3-dialkyl-substituted piperidine.

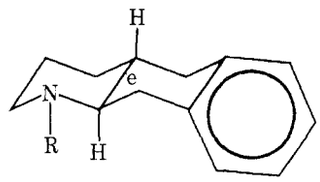
Scheme I



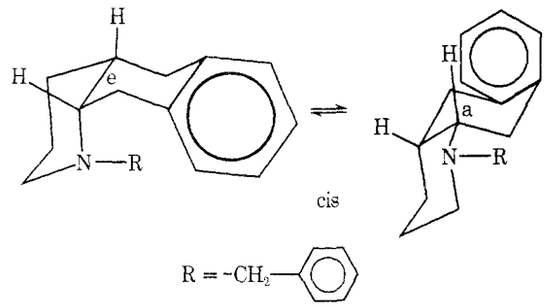
**6a**, $R_1 = H$
**b**, $R_1 = OCH_3$

**a.** cis, $R_2 = H$
**b.** trans, $R_2 = H$
**c.** cis, $R_2 = OCH_3$
**d.** trans, $R_2 = OCH_3$

* All correspondence should be addressed to D.A.W. at the Research Labs, A. H. Robins Co., Richmond, Va. 23220.
† Deceased, July 14, 1974.



trans

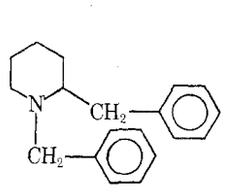


cis

R = -$CH_2$—

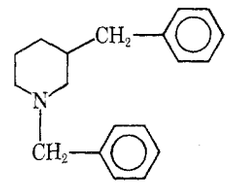
In the rigid trans isomer, the *N*-benzyl group is always adjacent to an equatorial alkyl substituent and the benzylic signal should appear as an AB quartet having a large (~60 Hz) chemical shift difference. The cis series is mobile and can undergo ring flip; thus the *N*-benzyl group is adjacent to a 2-equatorial and 3-axial substituent only part of the time. The benzyl signal would be expected to appear as a singlet or as an AB quartet having a relatively small chemical shift difference. The *N*-benzyl substituent could provide a convenient and absolute probe for determining the configuration of the octahydrobenzo[*g*]quinoline series.

The literature provided ample evidence to encourage our continued study. Compounds **9, 10,** and **11** can be considered mobile analogs of **1.** Pridgen[5] has determined that the



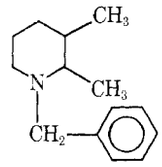
**9**

$J_{AB}$ = 13.5 Hz
$\Delta\nu$ = 34.9 Hz



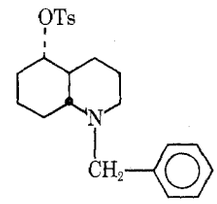
**10**

$J_{AB}$ = 13.0 Hz
$\Delta\nu$ = 12.9 Hz



**11a** cis
$J_{AB}$ = 13.8 Hz
$\Delta\nu$ = 7.9 Hz

**11b** trans
$J_{AB}$ = 13.5 Hz
$\Delta\nu$ = 43.0 Hz

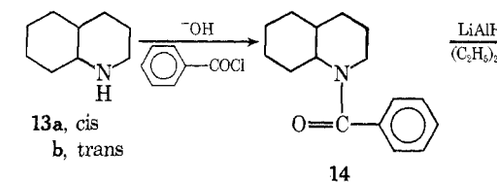


**12**

AB quartet for the benzylic protons of **11b** has a larger chemical shift difference than that for **11a.** In addition, Johnson, *et al.*,[6] observed that the nmr signal for the benzylic protons of **12** is an AB quartet.

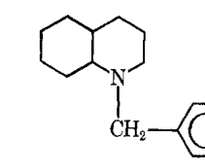
The *N*-benzyl derivatives of *trans*-decahydroquinoline and a mixture of *cis*- and *trans*-decahydroquinoline were prepared.

It has been demonstrated by Johnson[7] and Paulsen[8] that there is a serious steric interaction between an amide group and an adjacent equatorial group in the piperidine ring system. Such steric interactions are sufficient to cause conformational bias, resulting in the preference for axial configuration for the alkyl groups. The rigid *trans*-decahydroquinoline cannot undergo ring flip to alleviate this steric interaction as can the cis isomer. This steric interaction helps explain Johnson's[6] observation that for **16,** the isomer having the cis-ring juncture (**16a**) is the thermodynamically more stable isomer. The *N*-benzyl signal of **15b** appears as an AB quartet with a chemical shift difference of 61.4 Hz. The nmr spectrum of a mixture of **15a** and **15b** showed two AB quartets for the *N*-benzyl signals, one having a chemical shift difference of 23.7 Hz and the other a difference of 60.3 Hz, respectively.

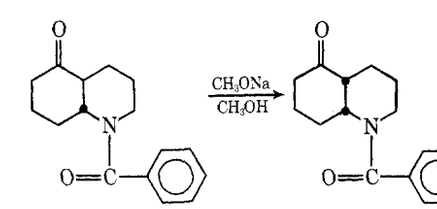


**13a,** cis
**b,** trans

**14**



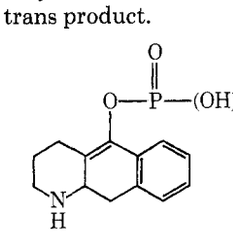
**15a,** $J_{AB}$ = 13.4 Hz
$\Delta\nu$ = 23.7 Hz
**15b,** $J_{AB}$ = 13.4 Hz
$\Delta\nu$ = 61.4 Hz



**16b** **16a**

The ketones **8b** and **8d,** prepared by cyclization with PPA, were subjected to catalytic reduction to give **1a** and **1b.** The benzyl derivatives **1e** and **1f** were then prepared. The benzylic signal appeared as an AB quartet with a chemical shift difference of 59.3 Hz for **1e** and 61.6 Hz for **1f,** substantiating that only the trans isomer was obtained from PPA cyclization.

Cyclization in strong acid results in carbonium ion formation, while cyclization in PPA could result in formation of significant amounts of a phosphate ester intermediate, **17,** which on hydrolysis would lead to the more thermodynamically stable trans product.



**17**

## Experimental Section

**Materials and Methods.** *trans*-Decahydroquinoline and a mixture of *cis*- and *trans*-decahydroquinoline were purchased from Eastman Chemical Co. The nmr spectra were determined in $CDCl_3$ using a Varian Model T-60 spectrometer, and the chemical shifts are given in $\delta$ units measured from TMS as an internal standard. All coupling constants and chemical shift differences are calculated at 100-Hz sweep width. The ir spectra of liquids were recorded as films and of solids as KBr pellets on a Perkin-Elmer Model 727 spectrophotometer. Elemental analyses were determined by James Haug of these Laboratories using a Hewlett-Packard Model 185B C, H, N analyzer. Melting points were taken in open capillaries on a Thomas-Hoover Uni-Melt apparatus and are uncorrected.

***cis*- and *trans*-1-Benzyloxycarbonyl-2-benzyl-3-piperidinecarboxylic Acid (6a).** A solution of 5.3 g (0.014 mol) of a mixture of ethyl *cis*- and *trans*-1-benzyloxycarbonyl-2-benzyl-3-piperi-

dinecarboxylate[2b] and 7.0 g (0.123 mol) of KOH in 150 ml of ethanol was heated at reflux for 3 hr. The solvent was evaporated and the residue was dissolved in 100 ml of water. The aqueous solution was extracted twice with 50 ml of ether, and the aqueous layer was made acidic with concentrated HCl. The white solid which precipitated was collected by filtration, washed with water, and dried to yield 4.9 g (100%) of **6a.** Recrystallization of **6a** from 2-propanol gave a white solid, mp 178–180°: ir 3300–2700 (carboxyl OH), 1710 (carbamate C=O) and 1645 (carboxyl C=O) $cm^{-1}$; nmr $\delta$ 9.57 (s, 1, COOH), 7.15 (s, 10, aromatic).

*Anal.* Calcd for $C_{21}H_{23}NO_4$: C, 71.36; H, 6.56; N, 3.96. Found: C, 71.51; H, 6.85; N, 4.19.

***cis*- and *trans*-1-Benzyloxycarbonyl-2-(3,4-dimethoxybenzyl)-3-piperidinecarboxylic Acid (6b).** The above procedure with 6.0 g (0.014 mol) of a mixture of ethyl *cis*- and *trans*-1-benzyloxycarbonyl-2-(3,4-dimethoxybenzyl)-3-piperidinecarboxylate[3b] gave 5.6 g (100%) of **6b,** mp 154–156° (*i*-PrOH–$H_2O$): ir 3400–3000 (carboxyl OH), 1725 (carbamate C=O), and 1665 (carboxyl C=O) $cm^{-1}$; nmr $\delta$ 9.50 (s, 1, COOH), 7.26 (m, 5, aromatic), 6.70 (s, 3, aromatic), 3.81 (s, 3, $OCH_3$), 3.74 (s, 3, $OCH_3$).

*Anal.* Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.38. Found: C, 67.07; H, 6.84; N, 3.32.

***cis*- and *trans*-2-Benzyl-3-piperidinecarboxylic Acid (7a).** A solution of 4.2 g (0.012 mol) of **6a** in 250 ml of $CH_3OH$ was hydrogenated over 1.7 g of 5% Pd/C at 18 psi for 7 hr. The catalyst was removed by filtration, and the filtrate was evaporated to give 2.5 g (96%) of **7a** as a white solid, mp 269–271° dec: ir 1600 ($COO^-$) $cm^{-1}$; nmr $\delta$ ($D_2O$) 7.12 (s, 5, aromatic), 3.65–1.32 (m, 10, aliphatic).

*Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.38. Found: C, 71.11; H, 7.98; N, 6.23.

***cis*- and *trans*-2-(3,4-Dimethoxybenzyl)-3-piperidinecarboxylic Acid (7b).** The above procedure with 6.0 g (0.015 mol) of **6b** gave 3.9 g (98%) of **7b** as a white solid, mp 240° dec ($CH_3OH$–$H_2O$): ir 1580 ($COO^-$) $cm^{-1}$; nmr $\delta$ ($D_2O$) 6.54 (s, 3, aromatic), 3.42 (s, 6, $OCH_3$), 3.40–1.20 (m, 10, aliphatic).

*Anal.* Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.57; N, 5.01. Found: C, 64.34; H, 7.48; N, 5.23.

***cis*- and *trans*-7,8-Dimethoxy-5-keto-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (8c and 8d).** A solution of 0.47 g (1.7 mmol) of **7b** and 5 ml of 95% $H_2SO_4$ was heated on a steam bath for 0.5 hr. The reaction mixture was cooled and diluted with ice, and the solution was made basic with 50% $NH_4OH$. The base was extracted with ether, and the combined extracts were dried ($Na_2SO_4$) and evaporated to give 0.15 g (30%) of the base as a clear oil. The hydrochloride, mp 205–208° dec ($CH_3OH$–$Et_2O$) was prepared. The nmr spectrum of the base indicated that there was a mixture of **8c** and **8d** present; nmr $\delta$ 7.40 (s, 0.5, cis aromatic $H_6$), 7.37 (s, 0.5, trans aromatic $H_6$), 6.57 (s, 1, aromatic $H_9$), 3.83 (s, 6, $OCH_3$), 3.40–1.00 (m, 10, aliphatic).

***trans*-5-Keto-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrochloride (8b).** The procedure of Smissman, *et al.*,[3a] was modified to produce **8b.** A mixture of 2.2 g (0.01 mol) of **7a** and 35 g of PPA was heated with stirring on a steam bath for 1 hr. The yellow solution was cooled, diluted with 50 ml of ice water, and made basic with 10% NaOH. The basic solution was extracted three times with 75 ml ether, and the combined ether extracts were washed with water, filtered through $Na_2SO_4$, and treated with gaseous HCl. The resulting solid was collected by filtration, washed with ether, and dried to yield 1.7 g (72%) of **8b** · HCl, mp 206–209° dec (lit.[3a] mp 204–205° dec): ir 1675 (ketone C=O) $cm^{-1}$; nmr $\delta$ 7.85 (m, 1, aromatic $H_6$), 7.15 (m, 3, aromatic $H_7$, $H_8$, $H_9$), 4.09–1.00 (m, 11, aliphatic).

***trans*-7,8-Dimethoxy-5-keto-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (8d).** The above procedure with 1.4 g (5.0 mmol) of **7b** gave 1.2 g (81%) of **8d** · HCl, mp 210–212° dec ($CH_3OH$).

*Anal.* Calcd for $C_{15}H_{20}ClNO_3$: C, 60.50; H, 6.76; N, 4.70. Found: C, 60.24; H, 6.50; N, 4.94.

The base was obtained by partitioning the salt between 10% NaOH and $CH_2Cl_2$. The $CH_2Cl_2$ layer was dried ($Na_2SO_4$) and concentrated to give **8d** as white needles, mp 145–146° dec (EtOAc); ir 1670 (ketone C=O) $cm^{-1}$; nmr $\delta$ 7.37 (s, 1, aromatic $H_6$), 6.57 (s, 1, aromatic $H_9$), 3.85 (s, 3, $OCH_3$), 3.83 (s, 3, $OCH_3$), 3.27–1.10 (M, 10, aliphatic).

*Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.32; N, 5.35. Found: C, 69.06; H, 7.47; N, 5.27.

***trans*-1,2,3,4,4a,5,10,10a-Octahydrobenzo[*g*]quinoline (1a).** A solution of 2.1 g (0.009 mol) of **8b** in 200 ml of ethanol and 7 ml of 70% of perchloric acid was hydrogenated over 2.1 g of 10% Pd/C at 60 psi overnight. The catalyst was removed by filtration and the filtrate was concentrated until the perchlorate salt began to precipitate. Water was added and the salt was collected by filtration and recrystallized from 2-propanol to give 1.8 g (75%) of **1a** · $HClO_4$ as a white solid, mp 256–258° dec.

*Anal.* Calcd for $C_{13}H_{18}ClNO_4$: C, 54.26; H, 6.30; N, 4.87. Found: C, 54.50; H, 6.32; N, 4.58.

The base was obtained by partitioning the perchlorate between 50 ml of $CH_2Cl_2$ and 25 ml of 10% NaOH. The $CH_2Cl_2$ layer was dried ($Na_2SO_4$) and evaporated to give **1a** as a clear oil: ir 3300 (N–H) $cm^{-1}$; nmr $\delta$ 7.06 (s, 4, aromatic); 3.56–1.00 (m, 13, aliphatic). The hydrochloride, mp 275–276° dec (ethanol), was prepared from the base in the usual manner.

*Anal.* Calcd for $C_{13}H_{18}ClN$: C, 69.78; H, 8.11; N, 6.26. Found: C, 70.11; H, 8.29; N, 6.15.

***trans*-7,8-Dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (1b).** The above procedure with 1.0 g (3.8 mmol) of **8d** gave 1.0 g (77%) of **1b** · $HClO_4$, mp 279–281° dec. The base was obtained as white plates, mp 105–106° (hexane): nmr $\delta$ 6.36 (s, 2, aromatic), 3.69 (s, 6, $OCH_3$), 3.25–1.00 (m, 13, aliphatic).

*Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.61. Found: C, 73.11; H, 8.11; N, 5.51.

The hydrochloride, mp 235° dec (acetone–ether), was prepared from the base in the usual manner.

*Anal.* Calcd for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.86; H, 7.94; N, 4.65.

**General Procedure for the Preparation of Benzamides.** A mixture of 0.020 mol of the secondary amine, 0.022 mol of benzoyl chloride, 50 ml of 5% NaOH, and 25 ml of $CH_2Cl_2$ was vigorously stirred for 1.5 hr. The layers were separated and the aqueous phase was extracted twice with 15 ml of $CH_2Cl_2$. The combined $CH_2Cl_2$ layers were washed once with 25 ml of 5% NaOH, once with 25 ml of $H_2O$, twice with 25 ml of 1 *N* HCL, and once with 25 ml of $H_2O$. The $CH_2Cl_2$ solution was dried ($Na_2SO_4$) and concentrated to give the amide.

***trans*-1-Benzoyldecahydroquinoline (14b).** Using the above procedure, *trans*-decahydroquinoline (Eastman) gave a quantitative yield of **14b,** mp 51–53° (lit.[9] mp 54–55°): ir 1625 (-NHC=O) $cm^{-1}$; nmr $\delta$ 7.23 (s, 5, aromatic), 3.31 (m, 4, aliphatic), 2.20 (m, 12, aliphatic).

***cis*- and *trans*-1-Benzoyldecahydroquinoline (14a and 14b).** Using the above procedure, a mixture of *cis*- and *trans*-decahydroquinoline (Eastman) gave a 98% yield of a mixture of **14a** and **14b** as a brown oil. This mixture was used without further purification, ir 1625 (NHC=O) $cm^{-1}$.

***trans*-1-Benzoyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (1c).** Using the above procedure, **1a** gave an 85% yield of **1c** as white needles, mp 162–163° (*i*-PrOH): ir 1605 (NHC=O) $cm^{-1}$; nmr $\delta$ 7.26 (s, 5, aromatic), 8.95 (s, 4, aromatic), 4.32–1.12 (m, 12, aliphatic).

*Anal.* Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.27; N, 4.81. Found: C, 82.44; H, 7.09; N, 4.52.

***trans*-1-Benzoyl-7,8-dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (1d).** Using the above procedure, **1b** gave a 71% yield of **1d** as a white solid, mp 165–166° (EtOAc); ir 1610 (NHC=O) $cm^{-1}$; nmr $\delta$ 7.40 (s, 5, aromatic), 6.58 (s, 1, aromatic), 6.55 (s, 1, aromatic), 3.83 (s, 6, $OCH_3$), 3.62–1.30 (m, 12, aliphatic).

*Anal.* Calcd for $C_{22}H_{25}NO_3$: C, 75.18; H, 7.17; N, 3.99. Found: C, 75.23; H, 7.23; N, 3.78.

**General Procedure for the Reduction of the Benzamides.** A mixture of 0.01 mol of the amide, 0.02 mol of $LiAlH_4$, and 25 ml of anhydrous $Et_2O$ was heated at reflux for 5 hr. The excess $LiAlH_4$ was decomposed with 10% NaOH and the ether removed by decantation. The residue was washed thoroughly with ether, and the combined ether layers were evaporated to give the benzylamine.

***trans*-1-Benzyldecahydroquinoline (15b).** Using the above procedure, **14b** gave an 86% yield of **15b** as a yellow oil: nmr $\delta$ 7.09 (s, 5, aromatic), 3.50 (AB, $J_{AB}$ = 13.4 Hz, $\Delta V_{AB}$ = 61.4 Hz, 2, $NCH_2Ph$), 2.80–0.80 (m, 16, aliphatic). The hydrochloride, mp 199–201° (*i*-PrOH–$Et_2O$), was prepared in the usual manner.

*Anal.* Calcd for $C_{16}H_{24}ClN$: C, 72.29; H, 9.10; N, 5.27. Found: C, 72.05; H, 9.20; N, 5.07.

***cis*- and *trans*-1-Benzyldecahydroquinoline (15a and 15b).** Using the above procedure, a mixture of **14a** and **14b** gave a 65% yield of a yellow oil which was determined by nmr to be a mixture of **15a** and **15b:** nmr $\delta$ 7.20 (s, 5, aromatic), 3.53 (AB, $J_{AB}$ = 13.4 Hz, $\Delta V_{AB}$ = 60.3 Hz, trans N–$CH_2Ph$), 3.53 (AB, $J_{AB}$ = 13.4 Hz, $\Delta V_{AB}$ = 23.7 Hz, cis N–$CH_2Ph$), 2.80–0.80 (m, 16, aliphatic).

***trans*-1-Benzyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (1e).** Using the above procedure, **1c** gave an 83% yield of **1e** as

a white solid, mp 86–87° (EtOH): nmr $\delta$ 7.16 (s, 5, aromatic), 6.93 (s, 4, aromatic), 3.63 (AB, $J_{AB}$ = 13.4 Hz, $\Delta V_{AB}$ = 59.3 Hz, 2, N–$CH_2$Ph), 3.60–0.80 (m, 12, aliphatic).

*Anal.* Calcd for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.47; H, 8.41; N, 4.83.

***trans*-1-Benzyl-7,8-dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (1f).** Using the above procedure, **1d** gave an 87% yield of **1f** as a clear oil: nmr $\delta$ 7.20 (s, 5, aromatic), 6.61 (s, 1, aromatic), 6.54 (s, 1, aromatic), 3.89 (s, 6, $OCH_3$), 3.71 (AB, $J_{AB}$ = 13.4 Hz, $\Delta V_{AB}$ = 61.6 Hz, 2, N–$CH_2$Ph), 3.60–0.80 (m, 12, aliphatic). Conversion of the base to the hydrochloride, mp 159–161° ($H_2O$), and reconversion of the salt to the base gave an analytically pure sample of **1f**.

*Anal.* Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.63; H, 7.98; N, 4.11.

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**Registry No.**—**1a,** 53011-21-5; **1a** $HClO_4$, 53011-22-6; **1a** HCl, 53011-23-7; **1b,** 53011-24-8; **1b** $HClO_4$, 53011-25-9; **1b** HCl, 53011-26-0; **1c,** 53011-27-1; **1d,** 53011-28-2; **1e,** 53011-29-3; **1f,** 53011-30-6; **1f** HCl, 53011-31-7; *cis*-**3a,** 53011-32-8; *trans*-**3a,** 53060-09-6; *cis*-**3b,** 53011-33-9; *trans*-**3b,** 53011-34-0; *cis*-**6a,** 53011-35-1; *trans*-**6a,** 53011-36-2; *cis*-**6b,** 53011-37-3; *trans*-**6b,** 53011-38-4; *cis*-**7a,** 53011-39-5; *trans*-**7a,** 53011-40-8; *cis*-**7b,** 53011-41-9; *trans*-**7b,** 53011-42-0; **8b,** 53011-43-1; **8b** HCl, 41191-52-0; **8c,** 53011-44-2; **8c** HCl, 53011-45-3; **8d,** 53011-46-4; **8d** HCl, 53011-47-5; **13a,** 10343-99-4; **13b,** 767-92-0; **14a,** 5710-04-3; **14b,** 22218-33-3; **15a,** 53011-48-6; **15b,** 784-85-0; **15b** HCl, 784-85-0; benzoyl chloride, 98-88-4.

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# Sodium Borohydride Reduction of Sterically Hindered Pyridinium Salts[1]

Robert E. Lyle*[2] and Charles B. Boyce

*Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824*

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The sodium borohydride reduction of 1-triphenylmethylpyridinium salts gave a mixture of dihydropyridines, with the 1,2 isomer predominating. Thermal decomposition gave loss of triphenylmethane and the original pyridine, suggesting the use of this derivative for protection of the pyridine ring during hydride reductions. The 2-hydroxyimino-1,1-dimethylethylpyridinium salts gave largely the tetrahydropyridine with sodium borohydride. Thermal or basic decomposition of the product removed the nitrogen substituent to give the 1-unsubstituted-1,2,3,6-tetrahydropyridine. This constitutes the only satisfactory reductive procedure for the synthesis of such compounds.

The mechanism of the reduction of pyridinium ions by sodium borohydride has been well defined, and the effect of substituents on the heterocyclic ring has been explored and can be predicted to some extent.[3] A large nitrogen substituent, because of steric interference to approach of the hydride reagent, causes the reduction to occur to a greater extent at the 4 position and gives the saturated piperidine. A nitrogen substituent with a $\pi$ bond which can overlap the occupied p orbital of nitrogen stabilizes the intermediate dihydropyridine by decreasing the nucleophilicity of the enamine system.

Synthetic methods were found for preparing two unusual salts of pyridine, the triphenylmethyl- and 2-hydroxyimino-1,1-dimethyl ethyl salts, and examples of these salts were studied with sodium borohydride. The products from these reductions provide interesting applications to organic syntheses.[4]

Pyridine was reported to undergo reaction with triphenylmethylcarbonium ion to form a pyridinium salt with the large triphenylmethyl group on the nitrogen. An improved method of synthesis was used to prepare 1-triphenylmethylpyridinium fluoroborate (**1**) in yields of about 85%. The reduction of 1-triphenylmethylpyridinium fluoroborate (**1**) with sodium borohydride gave a mixture of the 1,4- and 1,2-dihydropyridine (**2** and **3**) which did not undergo further reduction. Addition of water to the solution caused the precipitation of the dihydropyridines which then could be analyzed by the nuclear magnetic resonance spectrum. In this manner a very high yield of crude material was obtained which was shown to be 23% of the 1,4-dihydropyridine (**2**) and 77% of the 1,2-dihydropyridine (**3**). The compounds rapidly underwent decomposition on warming to give pyridine and triphenylmethane. The presence of 1,2-dihydropyridine (**3**) as the predominant product was further demonstrated by the successful Diels–Alder reaction using *N*-phenylmaleimide to give **4**. The stereochemistry and structure of **4** are based on the nmr spectrum. The endo stereochemistry would be expected, and the low-field signal for 2 hydrogens centered at 3.1 ppm suggest that these hydrogens are anti to the double bond.

The attempts to carry out similar reactions with substituted pyridines were less successful. The preparations of 1-triphenylmethyl-3-cyanopyridinium fluoroborate and 1-triphenylmethyl-3-methylpyridinium fluoroborate were accomplished; however, the products could not be obtained in analytical purity. The sodium borohydride reduction reactions on the crude compounds indicated the presence of large amounts of 1,2-dihydropyridine; however, the results were not conclusive.

A second series of pyridinium salts were formed by the reaction of 2-chloro-2-methylpropionaldehyde oxime, formed from isobutylene and nitrosyl chloride, with pyridines. The 1-(2-hydroxyimino-1,1-dimethylethyl)pyridinium chlorides prepared by this method are shown in Table I.

The sodium borohydride reduction of these pyridinium