Conformational Mobility of Dibenzo[a,d]cycloheptene Derivatives. Preparation and Characterization of Two Intraconverting Conformational Isomers

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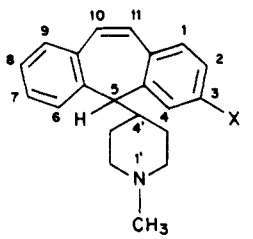
The boron trifluoride mediated triethylsilane reduction of 1-methyl-4-(5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)piperidines gives 5-substituted 5*H*-dibenzo[*a*,*d*]cycloheptenes of unexpected conformation. These unstable pseudoequatorially substituted compounds **1b** and **2b** undergo equilibration to the less hindered pseudoaxial conformers **1a** and **2a** through a thermally promoted ring flip. The $\Delta G^{\ddagger}$ for this isomerization as measured by kinetic NMR methods is shown to be approximately 25 kcal mol^{-1}. The structures of these conformers were assigned by means of NOE and single-crystal X-ray methods.

Introduction

Dibenzo[*a*,*d*]cycloheptene derivatives that bear substituents on the central seven-membered ring often suffer restricted conformational mobility, and, as a consequence, exhibit interesting stereochemical and pharamcological properties.[1a-h] Recently, we prepared a series of nuclear substituted 1-methyl-4-(5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)piperidine derivatives (**1**). Although the parent compound **1** is known,[2a,b] no other derivatives appear to have been prepared nor has the stereochemistry of the parent system **1** been studied. In this paper, we now report that two distinct isolable conformational isomers of **1** and the 3-bromo substituted compound **2** have been prepared. Further, we report on the structural assignment of these conformers by observation of nuclear Overhauser effects, and the temperature dependent conversion of one of the conformers of both **1** and **2** to its more stable isomer. The assignment of absolute configuration of the (+) and (−)-isomers of **2a**, obtained by resolution of (±)-**2a**, through single-crystal X-ray diffraction methods is described, and the free energy of activation for the conversion of the less stable into the more stable conformers of **1** and **2**, as measured by NMR methods, has been calculated. The interesting slow calcium channel blocking activity of these compounds will be presented elsewhere.[1i,j]

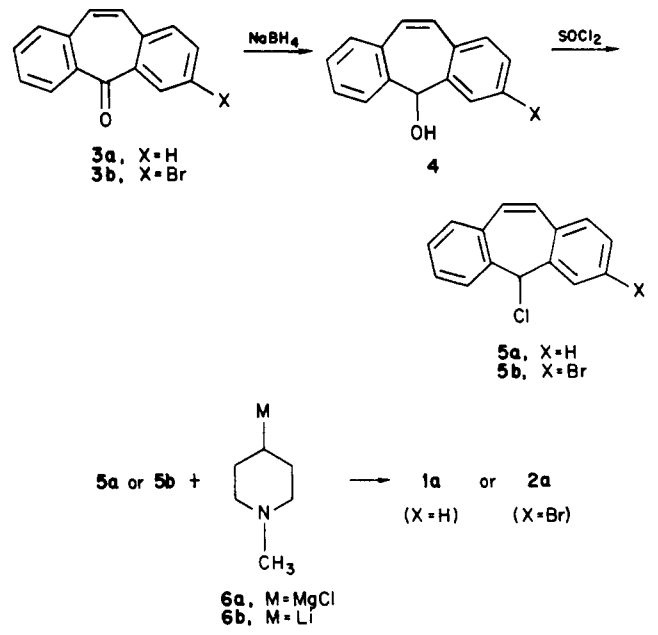


1, X = H
2, X = Br

Results

Preparation of 1-methyl-4-(5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)piperidine (**1a**) as described in the literature[1e] relies on displacement of dibenzylic chloride **5a**, with Grignard reagent **6a** or the corresponding lithium reagent **6b**.[2] Chloride **5a** is derived from dibenzosuberenone **3a** by borohydride reduction and subsequent chlorination of the alcohol with thionyl chloride (Scheme I). We examined an alternate route for the preparation of compounds **1** and **2** based on the alcohol **7a**.[1e,3] Of the known meth-

Scheme I



3a, X = H
3b, X = Br
4
5a, X = H
5b, X = Br
6a, M = MgCl
6b, M = Li

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(1) (a) Ebnöther, A.; Jucker, E.; Stoll, A. *Helv. Chim. Acta* **1965**, *48*, 1237. (b) Tochtermann, W. *Fortschr. Chem. Forsch.* **1970**, *15*, 378. (c) Tochtermann, W. *Chimia* **1972**, *26*, 565. (d) Murahashi, S.-I.; Moritani, I.; Nishino, M. *J. Am. Chem. Soc.* **1967**, *89*, 1257. (e) Engelhardt, E. L.; Zell, H. C.; Saari, W. S.; Christy, M. E.; Colton, C. D.; Stone, C. A.; Stavorski, J. M.; Wenger, H. C.; Ludden, C. T. *J. Med. Chem.* **1965**, *8*, 829. (f) Rokach, J.; Girard, Y.; Atkinson, J. G. *J. Chem. Soc., Chem. Comm.* **1975**, 602. (g) Oki, M. "Topics in Stereochemistry"; John Wiley and Sons: New York, 1983; Vol. 14, pp. 1-81. (h) Remy, D. C.; Rittle, K. E.; Hunt, C. A.; Anderson, P. S.; Arison, B. H.; Engelhardt, E. L.; Hirschmann, R.; Clineschmidt, B. V.; Lotti, V. J.; Bunting, P. R.; Ballentine, R. J.; Papp, N. L.; Flataker, L.; Witoslawski, J. J.; Stone, C. A. *J. Med. Chem.* **1977**, *20*, 1013. (i) Calcium slow channel entry blocking activity has been observed for the closely related compound cyproheptadine; see: Lowe, D. A.; Matthews, E. K.; Richardson, B. P. *Br. J. Pharmacol.* **1981**, *74*, 651. (j) Peroutka, S. J.; Allen, G. S. *Neurology* **1984**, *34*, 304.

(2) (a) Judd, C. J.; Drukker, A. E.; Biel, J. H. U.S. Pat. 2985660, 1961; *Chem. Abstr.* **1961**, *55*, 14621h. (b) The NMR spectrum for compound **1a** has not previously been reported. We include it here for reference: ^{1}H NMR ($CDCl_3$) δ 1.01 (4 H, m), 1.65 (2 H, m), 1.97 (1 H, m), 2.21 (3 H, s), 2.70 (2 H, br d, J = 12), 3.58 (1 H, d, J = 12), 6.88 (2 H, s), 7.26 (8 H, m).

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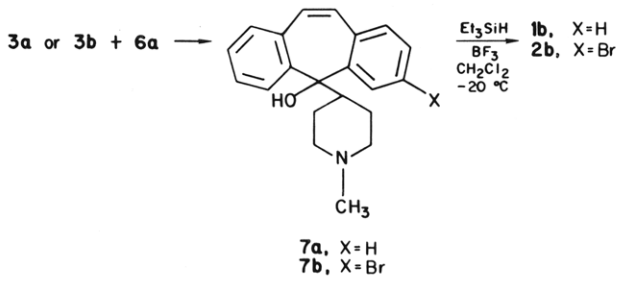
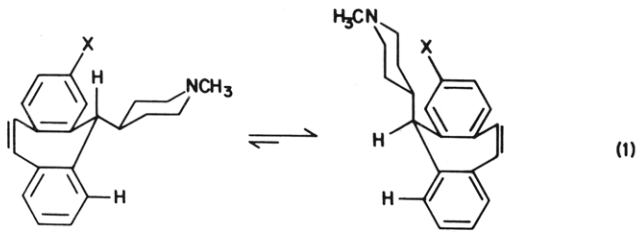
Scheme II



ods[4] for the reduction of benzylic alcohols to the associated hydrocarbon, the use of triethylsilane as a hydride donor seemed the most convenient. We examined the method reported by Kishi[4d] with triethylsilane with boron trifluoride as the catalyst. Treatment of a methylene chloride solution of alcohol **7a** and triethylsilane at −20 °C with boron trifluoride gas followed by aqueous workup, with the temperature at or below 0 °C (Scheme II), gives a compound (**1b**) whose ^{1}H NMR spectrum is consistent with the connectivity shown in structure **1** yet differs from the material prepared as outlined in Scheme I.

The melting point of compound **1b** was 127 °C. However, on remelting of the cooled sample the melting point had changed to 150–151.5 °C, identical with that of compound **1a**. Difference NOE measurements taken at 360 MHz showed an observable enhancement of the signal for the proton on carbon five, on saturation of the four and six aromatic protons in compound **1a**. No such enhancement could be observed for compound **1b**. However, an enhancement was seen for the 4-piperidine methine proton in compound **1b** on similar irradiation of the four and six aromatic protons. This data suggests that **1a** and **1b** are conformational isomers of each other as shown in eq 1.



(1)

The 3-bromo substituted compounds **2a** and **2b** were prepared (vide supra) and similar behavior was noted.

In order to quantify this phenomenon the kinetics for the thermal conversion of **1b** and **2b** into **1a** and **2a** respectively, were studied at several temperatures with NMR spectroscopy. A solution of either **1b** or **2b** was heated in an NMR probe at a constant temperature while spectra were obtained at regular intervals. The integrated intensities of the 5-axial proton in the starting material or the 5-equatorial proton in the product were fit to the following equation of exponential decay with a standard nonlinear least-squares approximation:[5]

$$Y = A_0 + A_1(1 - e^{-KT})$$

Y = observed intensity. A_1 = final intensity. T = time (in s). A_0 = initial intensity. K = rate constant (in s^{-1}).

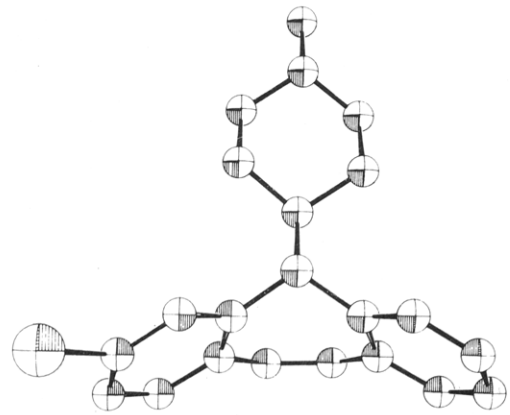


Figure 1. ORTEP stereo drawing of (−)-**2a**.

The values of the rate constant thus obtained were used to calculate the free energy of activation $\Delta G^{\ddagger}$ for the isomerization by application of the Eyring equation.[6] For the unsubstituted compound **1**, $\Delta G^{\ddagger}$ was found to be 25.1 kcal mol^{-1} at both 40 and 50 °C. For the 3-bromo compound **2**, $\Delta G^{\ddagger}$ was 25.3 kcal mol^{-1} at 35, 45, and 55 °C.

It should be noted here that the equilibrium constant in eq 1 lies far to the right. On heating either **1a** or **2a** for protracted periods no detectable amount of the less stable isomer is produced.

Substitution of one of the benzene rings, as in compounds **2**, produces a pair of enantiomers as carbon atom five is now a chiral center.

Our interest in the biological activity of these compounds related to cyproheptadine[1e,h,8] led us to develop a procedure for their resolution. We have resolved the stable isomer (±)-**2a** into its two enantiomers with D- and L-tartaric acids. The absolute configurations of (+)-**2a** and (−)-**2a** were established by single-crystal X-ray diffraction methods.[7] Figure 1 depicts (−)-**2a** indicating that C-5 has the "*R*" configuration.

Discussion

We have demonstrated that two stable conformational isomers of 4-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)piperidines can be synthesized and isolated.

The reduction of benzylic alcohols **7a**,**b** with triethylsilane–boron trifluoride, to give the less stable isomers of **1** and **2**, can be explained on the basis of steric demand of the reductant. When either alcohol **7a** or **7b** is treated with boron trifluoride a deep red color is produced, suggestive of the formation of a planar tropylium ion intermediate. Reduction of this planar species by the bulky triethylsiliane should result in an initially formed product where the piperidine ring remains in a pseudoequatorial conformation.

Measurement of the free energy of activation, $\Delta G^{\ddagger}$ for the thermally promoted isomerization of the less stable 5H-axial into the 5H-equatorial form gives values of approximately 25 kcal mol^{-1}. This value is well above the criteria described by Oki[1g] for isolation of atropisomers at 27 °C. Using a half-life of 1000 s for a rotamer as the minimum necessary for chemical isolation, Oki gives a value of 21.98 kcal mol^{-1} as the minimum free energy of activation. This value is given for the process that starts from an isomer which is the less favored one at equilibrium.

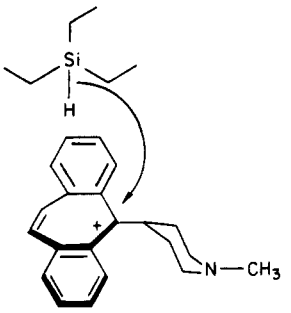
(3) Alcohol **7a** is the final intermediate in the industrial preparation of cyproheptadine (Periactin, Merck), a potent antihistaminic agent.

(4) (a) Frainnet, E.; Esclamadon, C. *Hebd. Sceances. Acad. Sci.* **1962**, *254*, 1814. (b) Doyle, M. P.; DeBruyn, D. J.; Kooistra, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 3659. (c) Adlington, M. G.; Orfanopoulos, M.; Fry, J. *Tetrahedron Lett.* **1976**, 2955. (d) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

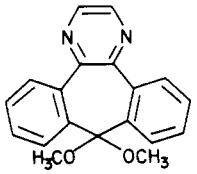
(5) Box, E. P. G. *N. Y. Acad. Sci. Ann.* **1960**, *86*, 792.

(6) Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107; *Chem. Rev.* **1935**, *17*, 65.

(7) The X-ray structure analysis was performed on a crystal of the (+)-enantiomer. The major portion of the biological activity resides in the (−)-enantiomer which is depicted in Figure 1 for clarity.



Although other examples of conformationally restricted dibenzo[a,d]cycloheptenes have appeared in the literature,[1f] to our knowledge, there are no reports of conformers that are stable enough to be isolated at room temperature. For example, Tochtermann[1b] reports observation of two methoxy signals in the NMR spectrum of pyrazinyl dibenzo[a,d]cycloheptene 8. These two signals apparently



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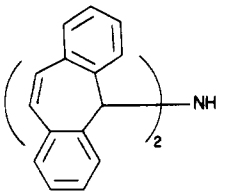

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arise from the pseudoboat conformation of the seven-membered ring. This gives rise to the axial and equatoral methoxy groups. Heating of the sample results in coalescence and from the coalescence temperature an activation energy of 19.7 kcal mol^{-1} was calculated. Rokach et al.[1f] have described the NMR spectrum of dimeric amine 9. It exhibits four singlets for the 5- and 5'-protons which collapse to a sharp singlet on heating. The four signals presumably arise from the three possible boat–boat conformers in solution. No attempt was made, however, to quantify this observation in terms of $\Delta G^{\ddagger}$.

In summary, single-crystal X-ray analysis has been used to unequivocally establish the absolute configuration of enantiomeric 4-(5*H*-3-bromodibenzo[a,d]cyclohepten-5-yl)piperidine **2a**. Two conformational isomers of dibenzo[a,d]cyclohepten-5-ylpiperidines have been synthesized and the activation energy for their intraconversion determined.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All reactions were conducted under a nitrogen atmosphere. Melting points (Pyrex capillary) were measured on a Thomas-Hoover apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer Model 1420 infrared ratio recording spectrophotometer. ^{1}H NMR spectra were determined on either a Varian EM390 or Nicolet NT360 spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in Hz. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter and concentration, *c*, is expressed in g per 100 mL. Elemental analyses were performed by the Analytical Department, Merck Sharp and Dohme Research Laboratories, West Point, PA.

(±)-(5*H*-*equatorial*)-1-Methyl-4-(3-bromo-5*H*-dibenzo-[*a*,*d*]cyclohepten-5-yl)piperidine (2a). To a solution of 3-bromodibenzo[a,d]cyclohepten-5-one[1e] (10.00 g, 0.035 mol) n absolute ethanol (100 mL) containing 0.1 mL of 10 N NaOH solution was added sodium borohydride (1.90 g, 0.05 mol) with stirring. This solution was stirred at 23 °C for 15 h. The ethanol was removed in vacuo and the residue was partitioned between ether and H_2O. The ether layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. This residue was dissolved in benzene (100 mL) to which thionyl chloride (10 mL) was added. The resulting solution was heated at reflux for 90 min, cooled to room temperature, and concentrated in vacuo. The residue was twice dissolved in benzene (50 mL) and concentrated to remove trace amounts of thionyl chloride. The crude chloride **5b** was dissolved in 75 mL of dry THF and the solution was cooled to 0 °C. To this solution was added a solution of (1-methylpiperidin-4-yl)-magnesium chloride[1e] in THF (35 mL of a 1 M solution, 0.035 mol) dropwise over 15 min. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was concentrated in vacuo to dryness and the residue was partitioned between toluene and H_2O. The toluene layer was washed with brine and dried ($MgSO_4$). Filtration and removal of the solvent in vacuo followed by chromatography of the residue on silica gel (3% methanol in chloroform) gave 4.50 g of piperidine **2a**. This material was recrystallized from hot acetonitrile to give 3.10 g of analytically pure material: mp 146–146.5 °C; IR ($CHCl_3$) 3000, 2820, 1585, 1300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (4 H, m), 1.64 (2 H, m), 1.90 (1 H, m), 2.17 (3 H, s), 2.68 (2 H, m), 3.48 (1 H, d, J = 11), 6.81 (1 H, d, J = 12), 6.92 (1 H, D, J = 12), 7.15–7.40 (7 H, complex multiplets). Anal. Calcd for $C_{21}H_{22}BrN$: C, 68.48; H, 6.02; N, 3.80. Found: C, 68.64; H, 6.12; N, 3.68.

(±)-1-Methyl-4-(3-bromo-5-hydroxy-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-yl)piperidine (7b). To a 500-mL 3-necked round-bottomed flastk with a mechanical stirrer, dropping funnel, and nitrogen inlet was added 3-bromodibenzo[a,b]cyclohepten-5-one[1e] (25.0 g, 87.6 mmol) and 250 mL of dry THF. The solution was cooled to 0 °C and a solution of 1-methylpiperidin-4-yl magnesium chloride in THF (100 mmol, 100 mL of a 1 M solution) was added to the well-stirred solution, dropwise. When the addition was complete the mixture was allowed to stir for 1 h at 0 °C. The reaction was quenched by addition of 150 mL of 15% aqueous ammonium chloride solution. The mixture was diluted with 500 mL of ether and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine. Drying (K_2CO_3), filtration, and removal of the solvent in vacuo left 20 g of crude alcohol **7b**. This material was recrystallized from hot acetonitrile to provide 17.7 g (52.4%) of analytically pure material: mp 207–208 °C; IR ($CHCl_3$) 3300, 2950, 2800, 1560, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75 (2 H, m), 1.31 (2 H, m), 1.64 (2 H, m), 2.16 (3 H, s), 2.51 (1 H, tt, J = 3, 12), 2.70 (2 H, m), 2.81 (1 H, s), 6.75 (1 H, d, J = 12), 6.90 (1 H, d, J = 12), 7.17 (1 H, d, J = 9), 7.25–7.45 (4 H, complex multiplets), 7.91 (1 H, dd, J = 2.5, 9), 8.11 (1 H, d, J = 2.5). Anal. Calcd for $C_{21}H_{22}BrNO$: C, 65.63; H, 5.77; N, 3.65. Found: C, 65.44; H, 5.92; N, 3.50.

(±)-(5*H*-*axial*)-1-Methyl-4-(3-bromo-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-yl)piperidine (2b). To a 500-mL 3-necked round-bottomed flask equipped with a mechanical stirrer, low temperature thermometer, and gas dispersion tube was added alcohol **7b** (2.0 g, 5.2 mmol), 100 mL of methylene chloride, and triethylsilane (1.0 g, 8.6 mmol). This solution was cooled to −25 °C and a steady stream of boron trifluoride gas was bubbled through the solution for 12 min. The mixture was allowed to warm to 0 °C and was maintained at that temperature for 2 h. The reaction was quenched by addition of solid potassium carbonate (10 g) and H_2O (100 mL). The layers were separated and the methylene chloride layer was washed with H_2O (2 × 100 mL) and brine (100 mL). Drying (K_2CO_3), filtration, and removal of the solvent left a residue which was chromatographed on 100 g of silica gel (4% methanol in chloroform) to provide 0.53 g (28%) of analytically pure **2b**: mp 131–132 °C; IR ($CHCl_3$) 2950, 2800, 1590, 1455, 1445 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (2 H, m), 2.14 (4 H, m), 2.30 (3 H, s), 2.65 (1 H, m), 2.70 (1 H, d, J = 10.5), 2.88 (2 H, m), 7.0–7.5 (9 H, complex multiplets). Anal. Calcd for $C_{21}H_{22}BrN$: C, 68.48; H, 6.02; N, 3.80. Found: C, 68.59; H, 6.19; N, 3.89.

(±)-(5*H*-*axial*)-1-Methyl-4-(5*H*-dibenzo[*a*,*d*]cyclo-hepten-5-yl)piperidine (1b). To a 250-mL 3-necked round-bottomed flask with a mechanical stirrer, low temperature thermometer, and gas dispersion tube was added alcohol **7a**[1e,3] (2.0 g, 6.5 mmol), 150 mL of methylene chloride, and triethylsilane (1.2 g, 10.3 mmol). This solution was cooled to −35 °C and a steady stream of boron trifluoride gas was bubbled in for 6 min during which time the reaction mixture became deep red. The reaction mixture was allowed to warm to 0 °C and stir for 3 h. The reaction

was then quenched by addition of solid potassium carbonate (10 g) and H_2O (100 mL). The layers were separated and the organic phase was washed with H_2O (2 × 100 mL) and brine (100 mL). Drying (K_2CO_3), filtration, and removal of the solvent left a semisolid residue which was chromatographed on 100 g of silica gel (5% methanol in chloroform). The chromatographed residue was triturated with cold acetonitrile to give 1.4 g (74%) of analytically pure **1b**: mp 127 °C; IR ($CHCl_3$) 2950, 2800, 1600, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (2 H, m), 2.15 (4 H, m), 2.29 (3 H, s), 2.69 (1 H, m), 2.79 (1 H, d, J = 12), 2.87 (2 H, br d, J = 12), 7.17 (2 H, s), 7.30 (8 H, m). Anal. Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.87. Found: C, 87.28; H, 8.27; N, 5.07.

Resolution of (±)-(5*H*-*equatorial*)-1-Methyl-4-(3-bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)piperidine (2a). A mixture of 2.78 g (7.55 mmol) of **(±)-2a** and 1.13 g (7.55 mmol) of *l*-tartaric acid was dissolved in 160 mL of boiling H_2O. The solution was filtered and then was allowed to cool slowly. The material that crystallized was removed by filtration, was washed with H_2O, and was collected and dried to afford 0.87 g of salt having mp 232–234 °C and $[\alpha]^{25}_{589}$ −31.6° (*c* 1.847, pyridine). The combined filtrate and washings were concentrated to approximately 90 mL and on cooling, an additional 0.26 g of salt having mp 228–232 °C, $[\alpha]^{25}_{589}$ −30.0° (*c* 1.122, pyridine), crystallized. The salts were combined to give 1.13 g of material that was used in Step A. The combined filtrates and washings were evaporated to dryness and were used in Step B.

Step A. The above salt (1.13 g) was recrystallized two times from H_2O to afford 0.67 g of material having a constant rotation: $[\alpha]^{25}_{589}$ −34.6° (*c* 1.641, pyridine), mp 239–239.5 °C. This salt was converted to the free base with saturated sodium bicarbonate solution, and it was then extracted into ether. The ether phase was washed with H_2O, dried ($MgSO_4$), and filtered, and the ether was removed. Recrystallization from acetonitrile gave **(+)-2a**: mp 178–180 °C; $[\alpha]^{25}_{589}$ +26.9°; $[\alpha]^{25}_{578}$ +29.0°; $[\alpha]^{25}_{546}$ +37.2°; $[\alpha]^{25}_{436}$ +126° (*c* 0.583, $CHCl_3$). Anal. Calcd for $C_{21}H_{22}BrN$: C, 68.48; H, 6.02; N, 3.80. Found: C, 68.50; H, 6.15; N, 4.07.

Step B. The solid, obtained from evaporation of the combined filtrates and washings, was suspended in H_2O and was treated with a saturated solution of sodium carbonate. The mixture was extracted with ether to afford 0.85 g of free base. A mixture of this free base and 0.346 g of *d*-tartaric acid was dissolved in 26 mL of boiling H_2O. The material that crystallized on cooling was removed by filtration to give 0.56 g of salt having mp 231–234 °C and $[\alpha]^{25}_{589}$ +28.0° (*c* 1.38, pyridine). This material was crystallized twice from H_2O to give 0.26 g of salt having a constant rotation: $[\alpha]^{25}_{589}$ +34.1° (*c* 1.586, pyridine); mp 239–239.5 °C. This salt was converted into the free base as described in step A. Recrystallization from acetonitrile gave **(−)-2a**: mp 178–180 °C; $[\alpha]^{25}_{589}$ −27.4°; $[\alpha]^{25}_{578}$ −29.5°; $[\alpha]^{25}_{546}$ −38.0°; $[\alpha]^{25}_{436}$ −127° (*c* 0.559, $CHCl_3$). Anal. Calcd for $C_{21}H_{22}BrN$: C, 68.48; H, 6.02; N, 3.80. Found: C, 68.46; H, 6.24; N, 3.87.

Equilibration of 1b and 2b to 1a and 2a. A sample of the desired 5H-axial compound (**1b** or **2b**) (4 mg) was dissolved in 0.5 mL of deuteriochloroform in an NMR tube at room temperature. The sample was then heated to the desired temperature in the NMR probe and the spectra were obtained every 730 s with a pulse angle of 60° and a repetition rate of 4 s. The reaction rate was measured from the appearance or disappearance of the 5*H*-benzylic methine proton by using the integrated intensity of the doublet to measure the amount of product/reactant present.

X-ray Crystallographic Analysis of 5*H*-Equatorial Conformer (+)-2a. Suitable crystals of **(+)-2a** for X-ray diffraction studies were formed from an acetonitrile solution. The space group symmetry was $P2_12_12_1$ with a = 9.663 (1) Å, b = 16.034 (2) Å, and c = 11.622 (2) Å for Z = 4. Of the 1439 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 1313 were observed ($I > 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined with full-matrix least-squares techniques.[8] The assignment of the absolute configuration was established by applying the anomalous scattering contributions for the non-hydrogen atoms. The correct enantiomer had an R factor of 0.0669 while the incorrect one was 0.0713. This difference is significant at the 0.005 level[9] and was confirmed by careful remeasurement of 10 enantiomorph sensitive reflections. Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum \omega (|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.036. Tables I, II, and III (supplementary material) contain the final fractional coordinates, temperature parameters, bond distances, and bond angles.

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Supplementary Material Available: Tables containing the fractional coordinates, temperature parameters, bond distances, and bond angles for **(+)-2a** (4 pages). Ordering information is given on any current masthead page.

(8) The following library of crystallographic programs was used: MULTAN 80, Univeristy of York, York, England, 1980; Structure Determination Package V18.0, Enraf-Nonius Corporation, Delft, Holland, 1981; ORTEP-11, Oak Ridge National Laboratory, Oak Ridge, TN, 1970.
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Temperature-Dependent Alkylation of γ-Phenyl β,γ-Unsaturated Acid and Ester Systems in Hexamethylphosphortriamide–Tetrahydrofuran Solutions Using Lithium Diisopropylamide

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The reactivities of some β,γ-unsaturated carboxylic acids and their methyl esters toward alkylation with methyl iodide using the lithium diisopropylamide–hexamethylphosphortriamide (LDA–HMPT) system in THF have been investigated. The methylation selectivity of pent-3-enoic acid (**2**) and (1,2-dihydro-3-naphthyl)acetic acid (**6**) on using 1.0 equiv of methyl iodide is high, the α-mono- to α,α-dimethylation ratios at −78 °C being >20. The selectivity is substantially lower for styrylacetic acid (**4**) and increases with increasing temperature from 2.3 at −78 °C to 8.5 at −10 °C. The occurrence of dimethylation is ascribed to intermolecular proton exchange between the monomethylated species IIa and the nonmethylated species Ia. For the β,γ-unsaturated esters the methylation selectivity is somewhat higher than that for the corresponding carboxylic acids.

Alkylation of charge-stabilized carbanions derived from compounds containing a reactive methylene group leads in most cases to a mixture of mono- and dialkylated products. To avoid the dialkylation, specific methods

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