Avondale, Pa.), total 20%, on Carbowax 4000 (W. H. Curtin & Co., Houston, Tex.). Helium was the carrier gas at a flow rate of 60–90 cm^3/min.

The ir spectra were obtained with a Perkin-Elmer 421 grating spectrometer by Mr. R. Swindlehurst of this department.

Solvents were removed by a rotary evaporator under water pump vacuum.

Reaction of NBS with 6,8-Dioxabicyclo[3.2.1]oct-3-ene, 1, or 6,8-dioxabicyclo[3.2.1]oct-2-ene, 2. To a solution of 8.96 g (0.08 mol) of **2**[4] in 400 ml of dry carbon tetrachloride was added 16.0 g (0.09 mol) of NBS along with a trace of peroxybenzoic acid catalyst. The mixture was heated under reflux for 3 hr, at which time the reaction was complete. The mixture was filtered from the supernatant succinimide and the solvent was removed from the filtrate. The residue, dissolved in 400 ml of ether, was washed thoroughly with a 10% aqueous solution of potassium carbonate and then with water. The collected water washings were extracted with ether (two 100-ml portions) and the combined ether solutions from the filtrate and extracts were dried ($MgSO_4$). Removal of the solvent and then the ether left a brown oil which was distilled in a micro fractional distillation apparatus to give 13.0 g (85%) of 4-*exo*-bromo-6,8-dioxabicyclo[3.2.1]oct-2-ene, **12**: bp 39–42° (0.05 mm), n^{25}D 1.5455.

Anal. Calcd for $C_6H_7O_2Br$: C, 37.72; H, 3.69; Br, 41.83. Found: C, 37.42; H, 3.97; Br, 42.02.

100-MHz pmr (CCl_4): δ 6.06 (d of d for H-2, $J_{1,2} \approx 4.5$ Hz, $J_{2,3} \approx 9.5$ Hz), 5.81 (d of q for H-3, $J_{3,5} \approx 1.8$ Hz, $J_{3,4} \approx 3.5$ Hz, $J_{3,2} \approx 9.5$ Hz, $J_{3,1} < 0.5$ Hz), 5.56 (narrow q for H-5, $W/2 \approx 3.5$ Hz, $J_{5,3} \approx 1.8$ Hz, $J_{5,4} \approx 0.5$ Hz), 4.68 (m for H-1, $J_{1,3} < 0.5$ Hz, $J_{1,2} \approx 4.5$ Hz), 4.63 (d of d for H-4, $J_{4,5} \approx 0.5$ Hz, $J_{4,3} \approx 3.5$ Hz, $J_{4,2} \approx 1.0$ Hz), 3.69 (two overlapping d for H-7 exo and H-7 endo, $J_{1,7\,endo} \approx 1.5$ Hz, $J_{1,7\,exo} \approx 3.0$ Hz, $J_{7\,exo,\,7\,endo} < 1.0$ Hz).

The reaction of *N,N*-dibromodimethylhydantoin with **2** gave an excellent yield of **12** as the only isolable product. Similar results were obtained by starting with compound **1**.

Reaction of 4-*exo*-Bromo-6,8-dioxabicyclo[3.2.1]oct-3-ene, 12, with Sodium Methoxide in Methanol. A solution of 5.73 g (0.03 mol) of **12** and 3.24 g (0.06 mol) of sodium methoxide in dry methanol was stirred while being heated under reflux for 80 hr. The mixture was then cooled and freed from methanol, and the residue was treated with 20 ml of water. The aqueous mixture was extracted repeatedly with ether and the combined ether extracts were dried ($MgSO_4$). Removal of the drying agent and ether gave an oily residue. Glc analysis of this crude material showed the presence of only two substances. Fractional distillation with a spinning-band column gave pure **13** (R = CH_3), bp 72–74° (2 mm), and pure **14** (R = CH_3), bp 67–69° (2 mm), in the proportion 2:1, respectively, and in a total yield of 70%. Products **13** and **14** were identical in all respects with the authentic compounds (see below).

Reaction of 4-*exo*-Bromo-6,8-dioxabicyclo[3.2.1]oct-2-ene, 12, with Aqueous Potassium Hydroxide. A mixture of the bromide **12** (7.64 g, 0.04 mol), 2.24 g (0.04 mol) of potassium hydroxide, and 100 ml of water was stirred at 90° for 48 hr and then heated under reflux for an additional 2 hr. The cooled solution was extracted continuously for 24 hr with methylene chloride. The organic layer was dried ($MgSO_4$) and then freed from solid and solvent, leaving an oily residue which distilled as a colorless oil, bp 49–53° (0.05 mm). Both glc and the pmr spectrum showed this oil to be a 1:1 mixture of only two substances. Attempts at separation by fractional distillation were unsuccessful. Glc separation resulted in decomposition of products. Only partial separation was obtained by the use of silica gel column chromatography.

The 100-MHz pmr spectrum of the mixture was identical with that of a 1:1 mixture of authentic **7**[7,8] and **9**.[10]

1,6-Anhydro-3,4-dideoxy-2-*O*-methyl-β-DL-*erythro*-hex-3-enopyranose, 14 (R = CH_3). Compound **14** (R = CH_3) was prepared by methylation of **7**[7,8] using the reported methylation procedure[17] with the following modification.

After the period of reflux, the solution was cooled and shaken with one-third of its volume of water. The aqueous layer was separated and extracted with ether (five 50-ml portions) to remove the somewhat water-soluble product. The ether extracts, combined with the organic layer from the cooled reaction mixture above, were dried ($MgSO_4$) and then freed from solid and solvent. The residue was distilled to give **14** (R = CH_3): yield 80%; bp 67–69° (2 mm); n^{25}D 1.4737.

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.43; H, 7.15.

100-MHz pmr (CCl_4): δ 6.14 (d of q for H-4, $J_{4,3} \approx 10$ Hz, $J_{4,5} \approx 4.5$ Hz, $J_{4,1} < 1.0$ Hz), 5.67 (d of q for H-3, $J_{3,4} \approx 10$ Hz, $J_{3,2} \approx 3.5$ Hz, $J_{3,5} \approx 1.8$ Hz), 5.38 (m for H-1, $W/2 \approx 4.0$ Hz, $J_{1,2} < 1.0$ Hz, $J_{1,3} \approx 2.0$ Hz), 4.56 (m for H-5, $J_{5,3} \approx 1.8$ Hz, $J_{5,4} \approx 4.5$ Hz, $J_{5,6\,endo} \approx 1.5$ Hz, $J_{5,6\,exo} \approx 2.5$ Hz), 3.52 (d for H-6 exo and H-6 endo, $J_{6\,exo,\,6\,endo} < 0.5$ Hz), 3.33 (s for CH_3), 3.21 (complex d for H-2, $J_{2,3} \approx 3.5$ Hz, $J_{1,2} < 1.0$ Hz).

1,6-Anhydro-2,3-dideoxy-4-*O*-methyl-β-DL-*erythro*-hex-2-enopyranose, 13 (R = CH_3). Compound **9**[10] was methylated by the same procedure used to prepare **14** above: yield 80%; bp 42° (0.1 mm); n^{25}D 1.4759.

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14: H, 7.09. Found: C, 58.98; H, 7.26.

100-MHz pmr (CCl_4): δ 6.04 (d of q for H-2, $J_{1,2} \approx 3.5$ Hz, $J_{2,3} \approx 10$ Hz, $J_{2,4} \approx 1.0$ Hz), 5.67 (d of q for H-3, $J_{3,2} \approx 10.0$ Hz, $J_{3,4} \approx 4.0$ Hz), at 5.34 (d for H-1, $J_{1,2} \approx 3.5$ Hz, $J_{1,3} < 0.5$ Hz), 4.58 (complex d for H-5, $J_{5,6\,exo} \approx 7.0$ Hz), 3.77 (d of d for H-6 exo, $J_{5,6\,exo} \approx 7.0$ Hz, $J_{6\,exo,\,6\,endo} \approx 8.0$ Hz), 3.35 (s for CH_3), 3.42–3.17 (complex m for H-4 and H-6 endo).

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Registry No.—**1**, 53152-84-4; **2**, 53152-85-5; **7**, 34685-53-5; **9**, 52630-80-5; **12**, 53111-75-4; **13** (R = Me), 53111-76-5; **14** (R = Me), 32445-57-1.

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Stereochemistry of the Reduction of α-Amino Ketones

Calvin L. Stevens,* Kenneth J. TerBeek,[1] and P. Madhavan Pillai

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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Although the stereochemistry of the reduction of α-hydroxy ketones has been extensively investigated,[2] the reduction of α-amino ketones has received very little attention. In a few instances where the reduction of α-dimethylamino ketones was reported,[3,4] only the trans amino alcohol was isolated and the stereochemistry of the reduction was not completely established. The reductions of monoalkylamino ketones with sodium borohydride have also been reported to give only trans amino alcohols except in one case involving a bicyclic ring system where a mixture of cis and trans amino alcohols was obtained.[5] The addition of Grignard reagents to acyclic amino ketones[2a,6] is known to yield products predicted by Cram's rule of "steric control

Table I
Summary of Experimental Data on the Amino Ketone Reductions

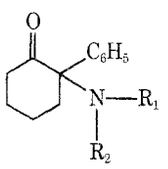
Amino ketone	Reducing agent	Solvent	Amino alcohols—Trans (%)	Amino alcohols—Cis (%)	Gc conditions[a]
1a	$NaBH_4$	EtOH	**2a** (100)	**3a** (0)	A
1b	$NaBH_4$	EtOH	**2b** (100)	**3b** (0)	A
	$Li(Me_3CO)_3AlH$	THF	**2b** (100)	**3b** (0)	A
	$LiAlH_4$	Et_2O	**2b** (100)	**3b** (0)	A
1c	$NaBH_4$	EtOH	**2c** (75)	**3c** (25)	B
	$Li(Me_3CO)_3AlH$	THF	**2c** (70)	**3c** (30)	B
	$LiAlH_4$	Et_2O	**2c** (80)	**3c** (20)	B
	B_2H_6	THF	**2c** (95)	**3c** (5)	B
1d	$NaBH_4$	EtOH	**2d** (100)	**3d** (0)	A, C
	$Li(Me_3CO)_3AlH$	THF	**2d** (100)	**3d** (0)	A, C
1e	$NaBH_4$	EtOH	**2e** (60)	**3e** (40)	B
	$Li(Me_3CO)_3AlH$	THF	**2e** (30)	**3e** (70)	B
1f	$NaBH_4$	EtOH	**2f** (100)	**3f** (0)	A
	$Li(Me_3CO)_3AlH$	THF	**2f** (100)	**3f** (0)	A
1g	$NaBH_4$	EtOH	**2g** (65)	**3g** (35)	A[b]
	$Li(Me_3CO)_3AlH$	THF	**2g** (15)	**3g** (85)	A[b]
1h	$NaBH_4$	EtOH	**2h** (100)		A[c]
1i	$NaBH_4$	EtOH	**2i** (100)		C[d]
	$Li(Me_3CO)_3AlH$	THF	**2i** (100)		C[d]

[a] The gc columns and the oven temperatures at which they were operated are the following: A, 10% phenyldiethanolamine succinate at 200°; B, 6% diglycerol at 125°; C, 15% SE 31 at 180°. [b] The structures of *trans*- and *cis*-2-(*N*-methyl-*N*-isopropyl)-2-phenylcyclohexanols are assigned tentatively on the basis of their gc retention times. [c] A small peak corresponding to *trans*-2-amino-2-phenylcyclohexanol was also obtained probably due to pyrolysis of **2h** at the injection port. [d] The reduction product was hydrogenated in the presence of 10% Pd/C and the resulting ethylamino alcohol[12] was analyzed.

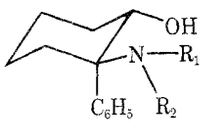
of asymmetric induction."[2a,7,8] We now report the reduction of several 2-amino-2-phenylcyclohexanones using a variety of hydride reagents. This study was undertaken to determine the stereochemistry of amino ketone reductions and to investigate the possibility of altering the stereochemical outcome by changing the substituents on the nitrogen atom or by employing different metal hydride reagents.

Results

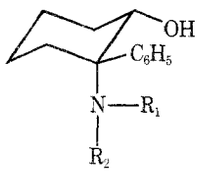
The synthesis of amino ketones **1a–f, 1h,** and **1i** has been reported previously.[4,9] 2-(*N*-Methyl-*N*-isopropyl)-2-phenylcyclohexanone (**1g**) was obtained by methylation of **1f** under Clark–Eschweiler conditions.[4] The syntheses of



1a-i



2a-i



3a-g

a, $R_1 = R_2 = H$
b, $R_1 = H$, $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$
d, $R_1 = H$, $R_2 = C_2H_5$
e, $R_1 = CH_3$, $R_2 = C_2H_5$
f, $R_1 = H$, $R_2 = i\text{-}C_3H_7$
g, $R_1 = CH_3$, $R_2 = i\text{-}C_3H_7$
h, $R_1 = H$, $R_2 = tert\text{-}C_4H_9$
i, R_1, $R_2 = -CH_2CH_2-$

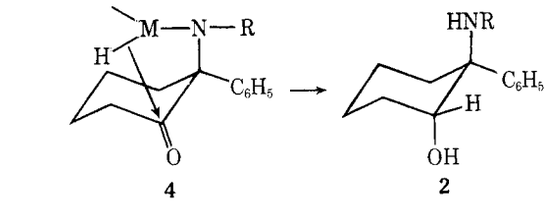
trans amino alcohols **2a–c, i** and the cis amino alcohols **3a, b** have also been recorded and their structures established.[4,9] The cis dimethylamino alcohol, **3c,** was prepared by the treatment of **3b** with ethyl chloroformate followed by reduction of the intermediate carbamate with diborane. Treatment of **2a** with acetic anhydride in pyridine and reduction of the resulting diacetate with diborane in tetrahydrofuran provided **2d** which was identical with a sample prepared by the reduction of **1d** with sodium borohydride.[4] Similarly, the cis ethylamino alcohol **3d** was obtained by acetylation of **3a** followed by reduction with diborane. The tertiary amino alcohols **2e** and **3e** were prepared by treatment of the corresponding ethylamino alcohols **2d** and **3d** with ethyl chloroformate and subsequent reduction of the carbamates with lithium aluminum hydride. Condensation of **2a** with acetone in the presence of *p*-toluenesulfonic acid and reduction of the imine gave the trans isopropylamino alcohol **2f** with the same characteristics as reported earlier.[4] The cis isomer **3f** was synthesized from **3a** by first treating it with 2,2-diethoxypropane in the presence of a small amount of *p*-toluenesulfonic acid followed by reduction of the intermediate oxazolidine with diborane. The *tert*-butylamino alcohol **2h** which was obtained by the reduction of amino ketone **1h** with sodium borohydride in ethanol[4] was shown to have trans configuration by its treatment with constant-boiling hydrobromic acid when the only basic material formed was *trans*-2-amino-2-phenylcyclohexanol (**2a**). Reduction of aziridino ketone **1i** with sodium borohydride provided *trans*-2(1-aziridinyl)-2-phenylcyclohexanol (**2i**) the stereochemistry of which was established by its hydrogenation in the presence of 10% palladium on carbon to give the trans ethylamino alcohol **2d.**[9]

The amino ketones were reduced with various reagents as listed in Table I. The crude reduction products were analyzed by gas chromatography and the components were identified and their ratios determined by comparison with standard mixtures of trans and cis amino alcohols previously synthesized. The results are summarized in Table I.

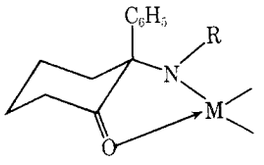
Discussion

It is clear from Table I that the primary and secondary amino ketones are reduced exclusively to the trans amino alcohols irrespective of the reducing agents used. This indicates that a stable complex (**4**) between the amine and the reducing agent is formed[10] and the reduction of the carbonyl group takes place by an internal hydride transfer.[11] It appears that the cyclic intermediate (**5**) as suggested in the reductions of α-hydroxy ketones by Cram and coworkers[2,7,8] is not a significant factor in these reductions. In the case of the bicyclic amino ketone **6,** the internal hydride transfer is hindered by the two-carbon bridgehead resulting in the reduction of the carbonyl group from both sides

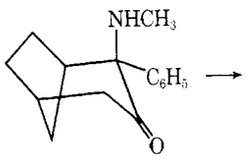
giving a mixture of trans and cis amino alcohols, **7** and **8**, respectively.



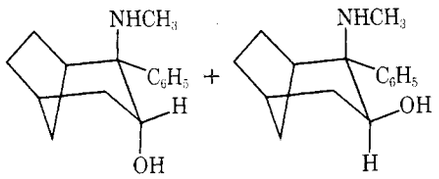
4 2



5



6



7 8

The nonstereoselectivity in the reduction of tertiary amino ketones may be explained as follows. The complex formed between the tertiary amine and the reducing agent is not as stable as that between a secondary amine and the reducing agent because a covalent bond is not possible in the former case. Consequently, the reduction of the keto group takes place both by hydride transfer and from hydride ions in solution. As the size of the substituents on the N atom and/or the reducing agent is increased, the stability of the amine-reducing agent complex is further weakened. In addition, a bulky amino group or a large reducing agent will hinder the approach of the hydride from the direction of the amine function, thus producing more of the cis amino alcohol.[12] This view is supported by the results of the reduction of amino ketones **1c**, **1e**, and **1g** with sodium borohydride and lithium tri-*tert*-butoxyaluminum hydride. The difference of the trans:cis ratio in the reduction of **1c** with sodium borohydride in methanol and diborane in tetrahydrofuran is due to the greater stability of the amine–borate complex in a nonhydroxylic solvent. The absence of the formation of a cis amino alcohol in the reduction of the aziridinyl ketone **1i** indicates that the complex between the aziridinyl group and the reducing agent is strong enough to effect the reduction almost exclusively by internal hydride transfer. The small, compact size of the aziridinyl group is probably responsible for the increased stability of this amine-reducing agent complex.[13]

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Thin-layer chromatography was performed using silica gel H from Brinkman Instruments coated on 5 × 15 cm glass plates. The developing solvent was $CHCl_3$–MeOH (9:1) unless otherwise mentioned. Compounds were detected by development with iodine vapor. Gas chromatographic analyses were performed on a F&M model 810 instrument fitted with a thermal conductivity detector. The columns used are given in Table I. The solid support was non-acid-washed chromosorb W. The nmr spectra were obtained using a Varian A-60 spectrometer with TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 237B grating spectrophotometer. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

2-(*N*-Methyl-*N*-isopropylamino)-2-phenylcyclohexanone (1g). A mixture of 86 mg (0.38 mmol) of amino ketone **1f**, 0.5 ml of 37% aqueous formaldehyde, and 4 ml of formic acid was heated on a steam bath for 24 hr. A tlc analysis indicated that the reaction was complete. The cooled mixture was diluted with 20 ml of H_2O, 0.5 ml of 6 *N* HCl was added, and then the mixture was extracted with ether to remove any neutral materials. The aqueous solution was made basic with NaOH, extracted with ether, dried (K_2CO_3), and evaporated to dryness to give **1g** as an oil. It was treated with picric acid in ether and the picrate salt was recrystallized from ethanol–ether to give 107 mg (64%), mp 190–192°.

Anal. Calcd for $C_{22}H_{26}N_4O_8$: C, 55.69; H, 5.52; N, 11.80. Found: C, 55.40; H, 5.66; N, 11.68.

***trans*-2-(*N,N*-Dimethylamino)-2-phenylcyclohexanol (2c) Hydrochloride.** Amino alcohol **2c** was prepared from *trans*-2-(*N*-methylamino)-2-phenylcyclohexanol (**2b**) by Clark–Eschweiler methylation as described previously.[4] It was converted to its hydrochloride and recrystallized from ethanol–ether; mp 220–221°.

Anal. Calcd for : C, 65.73; H, 8.67; Cl, 13.86; N, 5.47. Found: C, 65.98; H, 8.97; Cl, 13.86; N, 5.45.

***trans*-2-(*N*-Ethylamino)-2-phenylcyclohexanol (2d).** A solution of 100 mg (0.53 mmol) of **2a** in 5 ml of pyridine was acetylated with 0.5 ml of acetic anhydride overnight. The volatile materials were removed under reduced pressure; the residue was dissolved in ether; the ether solution was washed with water, dried (Na_2SO_4), and evaporated to dryness. The crude *O,N*-diacetate was dissolved in 10 ml of anhydrous THF, the solution was cooled to 0°, 8 ml of a 1 *M* solution of B_2H_6 in THF was added, and the mixture was heated under reflux for 2 hr under a nitrogen atmosphere. A cold, saturated solution of NH_4Cl was carefully added to the cooled solution followed by 6*N* HCl to break up any borate complex. The solvents were removed *in vacuo;* the residue was dissolved in 15 ml of water and extracted with $CHCl_3$ to remove neutral materials. The aqueous solution was made basic with NaOH, extracted with $CHCl_3$, dried (K_2CO_3), and evaporated to dryness. The residue was dissolved in ether and converted to the hydrochloride salt to give 75 mg (55% for two steps) of **2d** as its hydrochloride, mp 205–207°, after recrystallization from ethanol–ether. A mixture melting point with the $NaBH_4$ reduction product[4] of **1d** was undepressed.

***trans*-2-(*N*-Ethyl-*N*-methyl)-2-phenylcyclohexanol (2e).** A mixture of 130 mg (0.6 mmol) of amino alcohol **2d** in 10 ml of $CHCl_3$, 1.0 ml of ethyl chloroformate, and 150 mg of $NaHCO_3$ was stirred at room temperature for 3 hr. A tlc analysis showed that the reaction was complete. The inorganic materials were removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in 15 ml of dry THF, 150 mg of $LiAlH_4$ was added, and the mixture was heated under reflux for 3 hr. The product after the usual work-up was characterized as the hydrochloride salt (105 mg, 65%), mp 219–220° dec.

Anal. Calcd for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.86; Cl, 13.14; N, 5.19. Found: C, 66.16; H, 9.09; Cl, 13.53; N, 5.19.

***trans*-2-(*N*-*tert*-Butylamino)-2-phenylcyclohexanol (2h).** A mixture of 140 mg (0.5 mmol) of 2-(*N*-*tert*-butylamino)-2-phenylcyclohexanone (**1h**) hydrochloride[4] in 10 ml of ethanol and 100 mg of $NaBH_4$ was stirred at room temperature for 3 days. The product was isolated by the usual work-up and converted to the HCl salt to give 96 mg (69%) of **2h** as its hydrochloride salt, mp 202–203° dec. A mixture melting point with a sample prepared previously[4] was undepressed.

Anal. Calcd for $C_{16}H_{25}ClNO$: C, 67.90; H, 9.25; Cl, 12.49; N, 4.93. Found: C, 67.10; H, 9.15; Cl, 12.76; N, 4.93.

A solution of 96 mg (0.34 mmol) of **2h** (HCl) in 10 ml of constant-boiling hydrobromic acid was heated at 110° for 10 hr. The cooled mixture was diluted with water and extracted with ether to remove neutral by-products, mostly 2-phenylcyclohexanone.[14] The aqueous solution was made basic with NaOH, extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue on analysis by gc showed only one component corresponding to *trans*-2-amino-2-phenylcyclohexanol (**2a**). It was converted to the HCl salt to give 24 mg (32%) of **2a** (HCl), mp 199–200°. A mixture melting point with an authentic sample[4] was not depressed.

***cis*-2-(*N,N*-Dimethylamino)-2-phenylcyclohexanol (3c).** A mixture of 205 mg (1 mmol) of **3b** as the free base in 20 ml of $CHCl_3$, 2.5 ml of ethyl chloroformate, and 300 mg of $NaHCO_3$ was stirred at room temperature for 3 hr. The inorganic materials were

filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 25 ml of THF, 7 ml of a 1 *M* solution of B_2H_6 in THF was added, and the mixture was heated under reflux for 2 hr under a nitrogen atmosphere. Isolation of the product as described for the preparation of **2d** and conversion to the HCl salt gave 230 mg (90%) of **3c** (HCl), mp 204–206° dec.

Anal. Calcd for $C_{14}H_{22}ClNO$: C, 65.73; H, 8.67; Cl, 13.86; N, 5.47. Found: C, 65.96; H, 8.98; Cl, 13.57; N, 5.51.

***cis*-2-(*N*-Ethylamino)-2-phenylcyclohexanol (3d).** Acetylation of 193 mg (1 mmol) of **3a** with acetic anhydride in pyridine followed by reduction of the resulting *O,N*-diacetate with B_2H_6 in THF as described for the synthesis of **2d** gave 130 mg (59%) of **3d** as the free base, mp 99–100°, after recrystallization from hexane.

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.37. Found: C, 76.90; H, 9.74; H, 6.53.

***cis*-2-(*N*-Ethyl-*N*-methylamino)-2-phenylcyclohexanol (3e).** This compound was prepared from 60 mg (0.27 mmol) of **3d** using the same procedure for the conversion of **2d** to **2e.** The product was converted to the HCl salt (44 mg, 60%), mp 205–206°.

Anal. Calcd for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.86; Cl, 13.14; N, 5.19. Found: C, 66.67; H, 8.75; Cl, 13.13; N, 5.10.

Amino Ketone Reductions. In reductions with sodium borohydride, the free base was dissolved in ethanol, the solution was cooled to 0°, $NaBH_4$ was added in small portions, and the mixture was stirred overnight. After establishing the completion of the reaction by tlc, the mixture was diluted with water and acidified with 6 *N* HCl. The solvents were removed *in vacuo;* the residue was redissolved in water and extracted with ether. The aqueous layer was made basic with NaOH, extracted with ether, dried (K_2CO_3), and evaporated to dryness. When lithium tri-*tert*-butoxyaluminum hydride[15] was used as the reducing agent, the reductions were carried out in dry THF and the reagent was added in one lot. Otherwise the conditions were the same as for $NaBH_4$ reductions. In the case of $LiAlH_4$ reductions, ether was used as the solvent and the excess hydride was decomposed with wet ether. Amino ketone **1c** was also reduced with diborane. The procedure used is described under the synthesis of *trans*-2-(*N*-ethylamino)-2-phenylcyclohexanol (**2d**).

The reduction products without any further purification were analyzed by gc. The ratio of trans and cis amino alcohols was estimated from integration of the peaks corresponding to each component. Analysis of standard mixtures showed that this type of estimation was accurate within ±5%.

Registry No.—**1a,** 7015-50-1; **1b,** 7063-30-1; **1c,** 7015-60-3; **1d,** 6740-82-5; **1e,** 7062-18-2; **1f,** 7015-55-6; **1g,** 52906-46-4; **1g** picrate, 52906-47-5; **1h,** 52906-48-6; **1h** HCl, 7015-19-2; **1i,** 35099-65-1; **2a,** 52906-49-7; **2a** HCl, 7015-63-6; **2b,** 10275-95-3; **2c** HCl, 52906-50-0; **2d,** 52906-51-1; **2d** HCl, 7141-86-8; **2e** HCl, 52951-31-2; **2f,** 7015-72-7; **2g,** 52906-52-2; **2h** HCl, 7015-67-0; **2i,** 35099-66-2; **3a,** 52906-53-3; **3b,** 7015-29-4; **3c** HCl, 52949-44-7; **3d,** 52906-54-4; **3e** HCl, 52906-55-5; **3g,** 52906-56-6.

References and Notes

(1) Taken in part from the Ph.D. dissertation of K. J. TerBeek, Wayne State University, 1974.
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(9) C. L. Stevens, J. M. Cahoon, T. R. Potts, and P. M. Pillai, *J. Org. Chem.*, **37,** 3130 (1972).
(10) Stable borane–amine complexes have been isolated and used in the reduction of ketones in protic solvents. See, for example, (a) H. C. Kelly, M. G. Guisto, and F. R. Marchelli, *J. Amer. Chem. Soc.*, **86,** 3882 (1964); (b) S. S. White, Jr., and H. C. Kelly, *Ibid.*, **90,** 2009 (1968); **92,** 4303 (1970).
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(12) M. Akhtar and S. Marsh [*J. Chem. Soc. C,* 937 (1966)] have argued similarly to explain their results in the reduction of cholestan-5-α-ol-3-one.
(13) D. E. McLaughlin, M. Tamres, S. Searles, Jr., and F. Block [*J. Inorg. Nucl. Chem.*, **18,** 118 (1961)] isolated an *N*-methylaziridinetrimethylboron complex and showed that it was more stable than the complexes of trimethylboron with other cyclic tertiary amines.
(14) J. W. Stoddard, M. S. Thesis, Wayne State University, 1967.
(15) Purchased from Alfa Inorganics, Beverly, Mass.

The π-Electron Steric Effect

John P. Idoux,* V. S. Cantwell, J. Hinton, S. O. Nelson, P. Hollier, and R. Zarrillo

Department of Chemistry, Florida Technological University, Orlando, Florida 32816

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The study of substituent proximity effects and their influence on molecular properties have provided considerable information concerning the various contributory factors of these substituents and many of these studies have produced quantitative relationships which account for the influence of these factors.[1,2] On the other hand, Byron and his coworkers have reported[3] a nonquantitative, acid-weakening proximity effect of 2′-substituents in 2′-substituted biphenyl-4-carboxylic acids relative to a "normal" effect of 3′ and 4′ substituents in the corresponding 3′- and 4′-substituted biphenyl-4-carboxylic acids[4] and Dell'Erba and his coworkers have reported[5] similar observations for the rates of the piperidine-induced debromination of 2′-substituted 3-nitro-4-bromobiphenyls relative to the rates of debromination for the 3′- and 4′-substituted derivatives.[6] However, both groups of workers conclude that similar effects are not general for the 2′-substituted biphenyl system but rather depend upon the nature of the reaction center at the 4 position. This conclusion seems unlikely since the electron density about any reaction center at the 4 position should be altered by 2′ substituents if significant interactions, possibly of a π-electron steric origin, occur between the 2′ substituent and the π electrons of the ring carrying the reaction center. As an amino group would less readily accept an increase in electron density compared to the carboxylic acid, bromo, or other electronegative center, a study utilizing the amino group as the reaction center would be particularly suitable for investigating the π-electron steric effect of 2′ substituents in the biphenyl system. This paper reports such a study based on comparative pK_a values for a series of 2′- and 4′-substituted 4-aminobiphenyls and 4′-substituted 3-aminobiphenyls. In these series, "normal" alterations in pK_a should be produced by the 4′ substituents and also by the 2′ substituents if indeed a π-electron steric effect is insignificant.

The pK_a data for the three series of substituted aminobiphenyls are reported in Tables I and II. Inspection of these data indicates that the order and magnitude of the pK_a's for the two 4′-substituted series are identical within experimental error and can be rationalized in terms of expected, typical substituent effects. Correlation analyses[7,8] of the pK_a's *via* the Hammett equation gives $\rho = -0.67$, correlation coefficient $r = 0.930$, and standard deviation $s = 0.12$ for the 4′-substituted 4-aminobiphenyls and $\rho = -0.69$, $r = 0.939$, $s = 0.12$ for the 4′-substituted 3-aminobiphenyls. However, the pK_a data for the 2′-substituted 4-aminobiphenyls do not give a quantitative fit to the Hammett equation nor are the order and magnitude of these pK_a's "normal." That is, the 2′-acetamido group is base weakening relative to base strengthening by the 4′-acetamido groups, the 2′-hydroxy group is more strongly base strengthening than a 4′-hydroxy or methoxy group, and the 2′-nitro group is considerably less base weakening than in the 4′ position. These differences are attributed to a π-electron steric alteration in the "normal" effect of a substituent when the substituent is in the 2′ position.