THE JOURNAL OF Organic Chemistry

VOLUME 45, NUMBER 26

DECEMBER 19, 1980

Optical Rotatory Dispersion Studies. 133.[1] Deuterium Octant Contributions in Cyclohexanones

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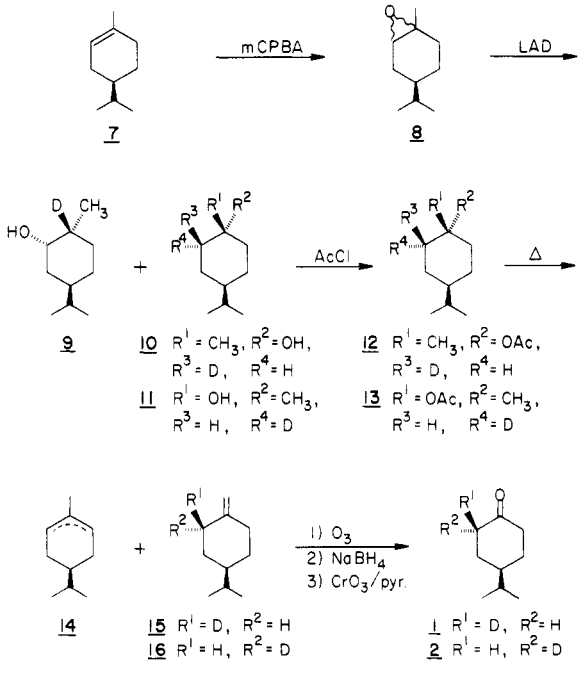
Received August 20, 1980

The synthesis of four conformationally rigid monodeuterium-substituted cyclohexanones, (2*R*,4*R*)-4-isopropyl(2-$^2H_1$)cyclohexanone (**1**), (2*S*,4*R*)-4-isopropyl(2-$^2H_1$)cyclohexanone (**2**), (3*R*,4*R*)-4-*tert*-butyl(3-$^2H_1$)-cyclohexanone (**3**), and (3*S*,4*R*)-4-*tert*-butyl(3-$^2H_1$)cyclohexanone (**4**), is described. The deuterium octant contributions as obtained from **1**–**4** for the α-equatorial, α-axial, β-equatorial, and β-axial positions are used to obtain estimates for the rotational strengths of the chair conformations of the conformationally flexible cyclohexanones (*R*)-(2-$^2H_1$)cyclohexanone (**5**) and (*S*)-(3-$^2H_1$)cyclohexanone (**6**). The predicted and experimental rotational strengths for **5** and **6** are found to be in good agreement.

The chiroptical properties of molecules which owe their asymmetry to isotopic substitution have been the subject of recent interest. From conformationally rigid ketones, substituted with deuterium in various positions, the octant contributions of the C–D bond have been established experimentally[2-4] and the results compared with those from theoretical calculations.[5] The variable-temperature circular dichroism measurements of conformationaly mobile monodeuterium-substituted cycloalkanones led to the quantitative evaluation of the steric isotope effect operating in these equilibria.[1,6-8] In a recent paper[4] we have reported the circular dichroism spectra of four conformationally rigid cyclohexanones, monodeuterium substituted in the α-equatorial [(2*R*,4*R*)-4-isopropyl(2-$^2H_1$)-cyclohexanone (**1**)], α-axial [(2*S*,4*R*)-4-isopropyl(2-$^2H_1$)-cyclohexanone (**2**)], β-equatorial [(3*R*,4*R*)-4-*tert*-butyl(3-$^2H_1$)cyclohexanone (**3**)], and β-axial [(3*S*,4*R*)-4-*tert*-butyl(3-$^2H_1$)cyclohexanone (**4**)] positions. In this publication we report the detailed syntheses of these compounds as well as the syntheses and circular dichroism spectra of conformationally mobile (*R*)-(2-$^2H_1$)cyclohexanone (**5**). Finally, the experimentally determined rotational strengths of **5** and (*S*)-(3-$^2H_1$)cyclohexanone (**6**)[9] are compared with

Scheme I



(1) For the preceding paper, see: Lee, S. F.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.*, in press.
(2) Lightner, D. A.; Chang, T. C.; Horwitz, J. *Tetrahedron Lett.* **1977**, 3019–3020. Errata. *Ibid.* **1978**, 696.
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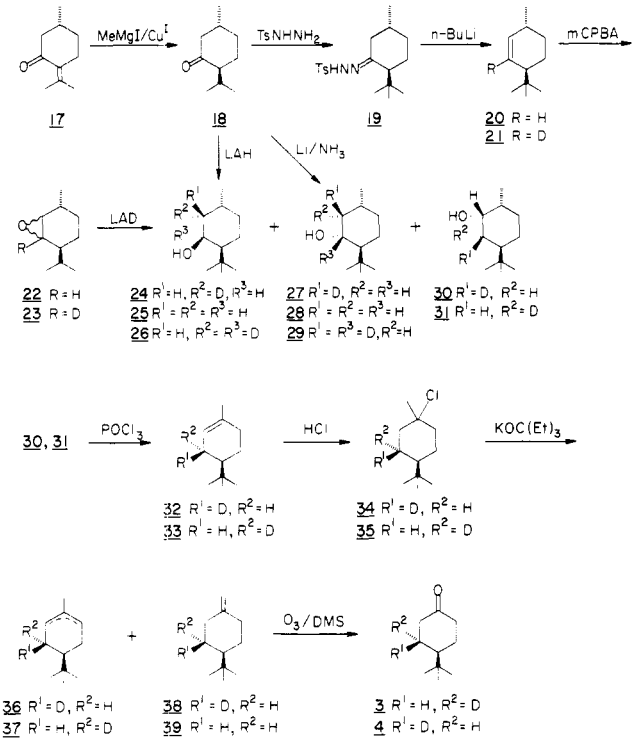
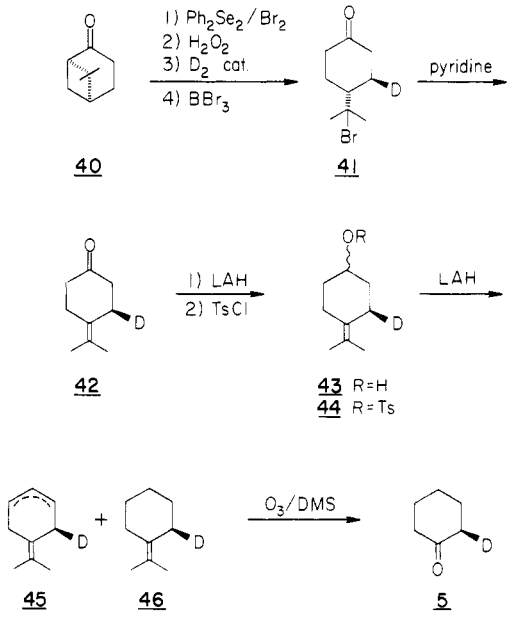
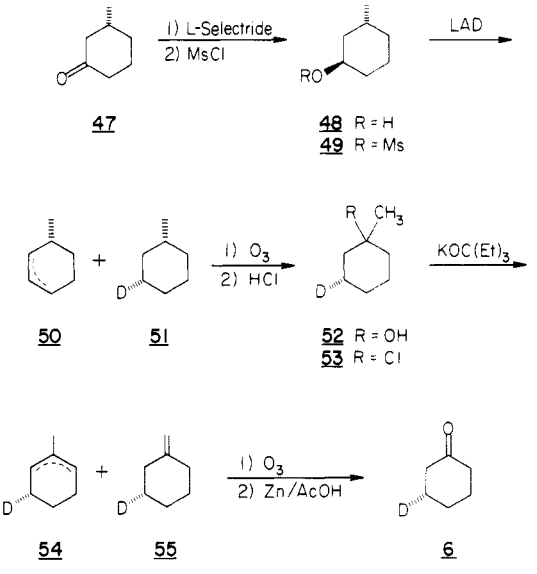
Scheme II



Scheme III



Scheme IV



the predicted values derived from the conformationally rigid reference compounds 1–4.

Synthesis

The α-equatorial (1) and β-axial (2) deuterium-substituted cyclohexanones were synthesized from (+)-*p*-menthene (7;[10] Scheme I; enantiomeric excess >95%). Epoxidation of 7 gave a mixture of epoxides 8 which upon reduction with lithium triethylborodeuteride[11] gave a mixture of three alcohols (9–11) whose stereochemistry was determined by ^{1}H NMR measurements[12] and by consideration of the S_N2 reaction mechanism of the epoxide ring opening. After column chromatographic separation the tertiary alcohols **10**[10] and **11**[10] were converted with acetyl chloride in *N,N*-dimethylaniline into their acetates **12** and **13**. Pyrolysis of the acetates gave the desired exocyclic olefins **15** and **16** in addition to the endocyclic analogue **14**. After purification, the olefins **15** and **16** were converted to **1** and **2** by ozonolysis. The synthesis of the β-equatorial (**3**) and β-axial (**4**) deuterium-substituted cyclohexanones is outlined in Scheme II. Epoxidation of the chiral olefin **20**,[13] derivable via **18** and **19** from (+)-pulegone (**17**; enantiomeric excess >95%), gave a mixture of epoxides **22** which was reduced with LAD in refluxing THF to a mixture of alcohols[14] **24**, **27**, and **30**. Their structures were determined by GLC retention time and ^{1}H NMR spectral comparison with (1*S*,2*S*,5*R*)-2-*tert*-butyl-5-methylcyclohexanol (**25**)[15] and (1*R*,2*S*,5*R*)-2-*tert*-butyl-5-methylcyclohexanol (**28**)[15] as obtained from (2*S*,5*R*)-2-*tert*-butyl-5-methylcyclohexanone (**18**) by reduction with LAH[15] and Li/NH_3,[16] respectively. The configuration of alcohol **30** was established by considering the chemical shift and shape[17] of the CHOH proton NMR signal which appears as a broad singlet ($w_{1/2}$ = 8.5 Hz) in **30**, **24**, and **25** and as a broad multiplet ($w_{1/2}$ = 23.0 Hz) in **27** and **28**. Dehydration of (1*S*,2*R*,5*R*,6*R*)-2-methyl-4-*tert*-butyl(6-^{2}H$_1$)-cyclohexanol (**30**) with $POCl_3$ in pyridine gave the endo olefin **32** which was transformed to the exo olefin **38** via the tertiary chloride **34** and dehydrochlorination. Ozonolysis of **38** followed by reductive workup gave the desired (3*S*,4*R*)-4-*tert*-butyl(3-^{2}H$_1$)cyclohexanone (**4**).

(3*R*,4*R*)-4-*tert*-Butyl(3-^{2}H$_1$)cyclohexanone (**3**) was obtained by slight modification of the above procedure. Decomposition of the tosylhydrazone **19** with *n*-BuLi in TMEDA[18] followed by quenching of the vinyl anion with D_2O gave the deuterated olefin **21** with 60% isotopic purity. By use of LAH instead of LAD in the reduction of

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Table I. Rotational Strengths and [Θ] Values for Deuterated Cyclohexanones 1-6

compd	deuterium orientation	[R],[a] [Θ] (λ, nm)	solvent[b]	lit. ref
1	α-equatorial	−0.03, −30 (299)	EPA	4
2	α-axial	−0.25, −298 (298)	IO	this study[c]
3	β-equatorial	0.27, 290 (298)	IO	19
4	β-axial	−0.03, −28 (297)	EPA	4
5		0.14, 143 (286)	EPA	this study[d]
6		0.15, 152 (297)	EPA	this study

[a] Values (measured at room temperature) are expressed as reduced rotational strengths and are corrected to 100% enantiomeric excess and isotopic purity. [b] EPA = ether-isopentane-ethanol, 5:5:2; IO = isooctane. [c] The previously reported [Θ] value of −0.13 for 2 was found to be too low, probably because of the facile α-proton exchange which this compound undergoes during any chromatographic purification. The value reported here was obtained on a sample purified through distillation only. [d] Repetition of the synthesis of 6 yielded a [Θ] value about three times larger than that reported previously,[9] most likely as a result of some chemical impurity. Dauphin et al.[31] have reported a [Θ] value of 122 for this compound, but according to a private communication from Dr. Kergomard, this value is lower than ours because of a minor chemical impurity.

the deuterated epoxides **23**, the deuterated alcohols **26**, **29**, and **31** were obtained. After column chromatographic purification (2*S*,3*R*,6*R*)-3-*tert*-butyl-6-methyl(2-$^2H_1$)-cyclohexanol (**31**) was converted to (3*R*,4*R*)-4-*tert*-butyl-(3-$^2H_1$)cyclohexanone (**3**) by using the same reaction steps as for the synthesis of (3*S*,4*R*)-4-*tert*-butyl(3-$^2H_1$)cyclohexanone (**4**).

The synthesis of (*R*)-(2-$^2H_1$)cyclohexanone (**5**) is given in Scheme III. (−)-Nopinone (**40**) (enantiomeric excess 90%) was converted to **41** as described previously.[19] Dehydrobromination in pyridine gave **42**, which was converted to (*R*)-isopropylidene(2-$^2H_1$)cyclohexane (**46**) via LAH reduction to **43**, tosylate formation to **44**, and renewed LAH reduction. After removal of the olefin impurity **45** derived from tosylate elimination, (*R*)-isopropylidene(2-$^2H_1$)cyclohexane (**46**) was converted to (*R*)-(2-$^2H_1$)cyclohexanone (**5**) by ozonolysis and reductive workup. (*S*)-(3-$^2H_1$)cyclohexanone (**6**) was synthesized according to Scheme IV.[9] Reduction of (*R*)-3-methylcyclohexanone (**47**), conveniently obtainable from (+)-pulegone[20] (enantiomeric excess >95%), with L-Selectride[21] furnished the trans alcohol **48** which was converted into its mesylate **49**.[22] Reduction of **49** with LAD gave **51** together with a mixture of olefins **50**. Purification of **51** on silver nitrate impregnated alumina[23] and dry ozonolysis[24] gave the tertiary alcohol **52** which was converted to the chloride **53** with HCl gas[25] and dehydrochlorinated with potassium triethylmethoxide[26] to a mixture of olefins **54** and **55**. Gas chromatographic purification of the desired (3*S*)-methylene(3-$^2H_1$)cyclohexane (**55**) followed by ozonolysis led to (*S*)-(3-$^2H_1$)cyclohexanone (**6**). The enantiomeric excess of the six deuterated cyclohexanones (**1**–**6**) was assumed to be equal to that of the starting materials.

Results and Discussion

The circular dichroism spectra of **1**–**4** and **6** have been reported in two preliminary papers,[4,9] and their rotational strengths and [Θ] values are listed in Table I. The circular dichroism spectra of the hitherto undescribed (*R*)-(2-$^2H_1$)cyclohexanone (**5**)[27] in two solvent systems of different polarity [EPA (ether–isopentane–ethanol, 5:5:2) and IPM (isopentane–methylcyclohexane, 4:1)] measured at room temperature and 77 K are reported in Figure 1. Within the experimental error, no changes of the rotational strength with temperature are observed,[28] the same result as obtained for **6**.[9] Whereas the vibrational fine structure of the C=O n → π* transition becomes well resolved at low temperature (Figure 1a) in EPA, the opposite is observed in IPM (Figure 1b); in addition, a three times larger blue shift (11 nm) is observed in the nonpolar solvent mixture. A priory, one would have expected the opposite behavior since, in general, the vibrational fine structure of an electronic transition is better resolved in a nonpolar solvent, but such an apparent anomaly has been observed previously by us.[8] We have interpreted it as resulting from the presence of a dimerization equilibrium which is favored in a nonpolar solvent. In support of this interpretation we draw attention to the absence of such an anomaly in α-dimethyl-substituted cyclohexanones;[6,7,29] i.e., their

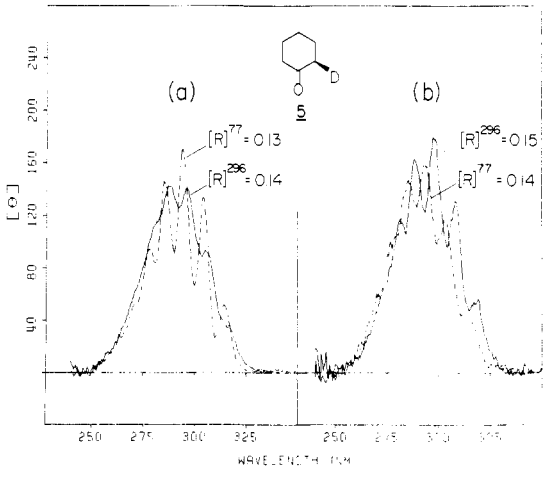

Figure 1. Circular dichroism spectra of (*R*)-(2-$^2H_1$)cyclohexanone (**5**) at room temperature (solid line) and 77 K (dashed line) in (a) EPA (ether–isopentane–ethanol, 5:5:2 vv) and (b) IPM (isopentane–methylcyclohexane, 4:1 vv). The spectra are corrected to 100% enantiomeric excess and isotopic purity.

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(28) Due to the presence of a steric isotope effect the equilibria of **5** and **6** are biased toward the conformations with the deuterium in the axial positions (i.e., $\mathbf{5}_{ax}$ and $\mathbf{6}_{ax}$) by a few calories per mole.[6,7,9] Assuming this value to be 5 cal/mol, the equilibrium composition of ax/eq would be 50.2:49.8 at room temperature and 50.8:49.2 at 77 K. Since $[R]_{ax}$ and $[R]_{eq}$ are relatively small numbers (Scheme V), the associated temperature variation of $[R]_{obsd}$ is below the experimental error limit (±0.005).

spectra are better resolved in IPM compared to those in EPA, and a larger blue shift is observed in the polar solvent mixture. Presumably the presence of the bulky dimethyl group restricts dimer formation.

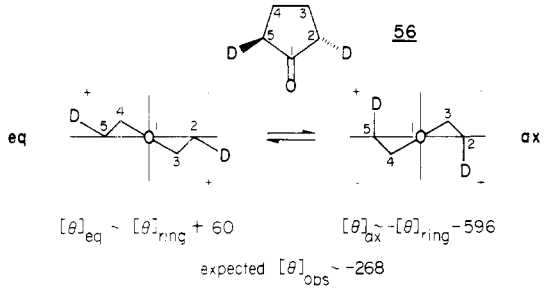
By using the rotational strengths of 1–4 as reference values ($[R]_{ax}$, $[R]_{eq}$) for the conformers participating in the chair ⇌ chair equilibria of **5** and **6** (Scheme V), we are now in a position to predict the rotational strength $[R]_{obsd}$ (eq 1) by assuming that both conformers are present in nearly

$$[R]_{obsd} = 0.5([R]_{ax} + [R]_{eq}) \quad (1)$$

equal amounts.[28] The obtained values (Scheme V) are in good agreement with the experimental ones (Figure 1), thereby confirming that, as far as chiroptical properties are concerned, the stereochemically rigid 4-isopropyl and 4-*tert*-butylcyclohexanones 1–4 are good models for the flexible chair conformations of (*R*)-(2-$^2H_1$)cyclohexanone (**5**) and (*S*)-(3-$^2H_1$)cyclohexanone (**6**).

Conclusion

With the availability of experimentally determined octant contributions of deuterium in the various positions of the cyclohexanone ring system, it is now possible to make fairly accurate predictions about the Cotton effect sign and amplitude for related compounds and to make structural assignments for deuterium-substituted molecules whose absolute stereochemistry is in question. This has already proven useful in determining the course of certain enzymatically induced deuterium substitutions in cycloalkanones.[30,31] A further interesting example has recently been described by Hine et al.[32,33] The α-deuterium exchange, catalyzed by a chiral base of (2,2,5,5-$^2H_4$)cyclopentanone yielded (2,5-$^2H_2$)cyclopentanone (**56**) which



exhibited a positive Cotton effect. By making assumptions about the configuration of the transition state, the authors assigned the 2*S*,5*S* configuration to this molecule. Assuming that both twist conformations of **56** (i.e., $\mathbf{56}_{ax}$ and $\mathbf{56}_{eq}$) are present in nearly equal amounts (i.e., that the ring contributions $[\Theta]_{ring}$ cancel) and by using the deuterium octant contributions obtained from the cyclohexanone analogues (i.e., **1** and **2**, Table I), one would, however, have predicted a negative Cotton effect.

The discrepancy between these conflicting assignments can ultimately be resolved only through an independent synthesis of **56** (or its monodeuterium-substituted analogue). Since this example would provide a good test for the general applicability of partial deuterium octant contributions in predicting the stereochemistry of chiral deuterium-substituted ketones, we are now in the process of synthesizing a chiral α-deuterium-substituted cyclopentanone of known absolute configuration.

Experimental Section

Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were determined on a Rudolph Autopol III polarimeter in a thermostated 1.00-dm cell with removable endplates in chloroform as solvent unless otherwise noted. Circular dichroism spectra were measured on a JASCO J-40 instrument using an earlier described[34] cell for the low-temperature measurements. ^1H NMR spectra were obtained on a Varian T-60 (60 MHz) spectrometer using (^2H)-chloroform as solvent and tetramethylsilane as internal standard. Low-resolution mass spectra were obtained on a Varian MAT-44 spectrometer. High-resolution mass spectra were determined by Ms. A. Wegmann on a Varian MAT-711 instrument.

Acetylation of (1*S*,2*S*,4*R*)-1-Methyl-4-isopropyl(2-$^2H_1$)-cyclohexanol (11). A solution of 11.3 g (70 mmol) of the alcohol **11**[10] in 50 mL of *N*,*N*-dimethylaniline and 7 mL of acetyl chloride was heated on a steam bath for 2 h. The reaction mixture was poured into water and extracted with ether. The ether layer was washed with diluted HCl, saturated sodium bicarbonate, and water, dried, and evaporated to yield 9.4 g (66%) of the acetate **13**: ^1H NMR 0.86 (d, *J* = 6 Hz, 6 H), 1.55 (s, 3 H), 1.96 (s, 3 H); mass spectrum, *m*/*z* (relative intensity) 139 (46, $M^+ - 60$), 96 (100), 82 (30), 69 (50), 68 (23), 43 (30).

Acetylation of (1*R*,2*R*,4*R*)-1-Methyl-4-isopropyl(2-$^2H_1$)-cyclohexanol (10). The alcohol **10**[10] (4.7 g, 30 mmol) was converted by the procedure given for **11** into the acetate **12**: ^1H NMR 0.86 (d, *J* = 6 Hz, 6 H), 1.58 (s, 3 H), 1.96 (s, 3 H); mass spectrum, *m*/*z* (relative intensity) 139 (47, $M^+ - 60$), 96 (100), 82 (30), 69 (50), 68 (20), 43 (23).

(2*S*,4*R*)-4-Isopropyl(2-$^2H_1$)cyclohexanone (2). Pyrolysis of the acetate **13** was effected by passage through an 11-in. Pyrex column packed with 5-mm glass beads and heated to 450 °C. The collected product (7.69 g) consisted of a mixture of the olefins **14** and **16** in a ratio of 3:1. The crude mixture of olefins **14** and **16** was ozonized in methanol at −78 °C. Reduction of the ozonide with a large excess of $NaBH_4$ gave a mixture of alcohols which were isolated and oxidized with CrO_3/pyridine. Standard workup and purification by distillation gave 80 mg of **2**: mass spectrum, *m*/*z* (relative intensity) 141 (60, M^+), 140 (12), 122 (18), 108 (28), 107 (12), 99 (20), 98 (42), 97 (22), 86 (24), 85 (52), 84 (38), 71 (20), 70 (62), 69 (88), 68 (20), 57 (44), 56 (82), 55 (100).

(2*R*,4*R*)-4-Isopropyl(2-$^2H_1$)cyclohexanone (1). This ketone was obtained from the acetate **12** by the same procedure as that described for the axial isomer **2**: mass spectrum, *m*/*z* (relative intensity) 141 (33, M^+), 140 (4), 122 (12), 108 (14), 99 (12), 98 (36), 97 (14), 86 (18), 85 (48), 84 (32), 70 (60), 69 (79), 57 (26), 56 (84), 55 (100).

Epoxidation of the Olefin 20. To a solution of 3.0 g (20 mmol) of (+)-(3*R*,6*R*)-3-*tert*-butyl-6-methylcyclohexene (**20**)[13] in 50 mL of dichloromethane cooled to 0 °C was added 4 g (23 mmol) of *m*-chloroperbenzoic acid in small portions over a period of 4 h. The reaction mixture was stirred for 8 h. After a standard workup, 2.79 g of a mixture of epoxides **22** was obtained: ^1H NMR 0.96 (s, 9 H), 1.10 (d, *J* = 6 Hz, 3 H), 3.05 (br s, 2 H); mass spectrum, *m*/*z* (relative intensity) 168 (2, M^+), 153 (26), 111 (48), 95 (24), 70 (50), 69 (36), 67 (24), 57 (100), 55 (80).

Reduction of Epoxides 22. To a suspension of 1 g of lithium aluminum deuteride in 50 mL of anhydrous ether was added dropwise a solution of 3.9 g (23 mmol) of the epoxides **22** in 50 mL of anhydrous ether. The reaction mixture was heated under reflux for 8 h, followed by hydrolysis with water, filtration, drying over anhydrous $MgSO_4$, and evaporation. Chromatography of the residue by preparative high-pressure LC using hexane/EtOAc (95:5) as eluting solvent gave the following three alcohols.

(1*S*,2*R*,3*R*,6*S*)-3-Methyl-6-*tert*-butyl(2-$^2H_1$)cyclohexanol (24): $[\alpha]^{25}_D$ +21.2° (*c* 0.0019); ^1H NMR δ 0.96 (overlapping s and d, *J* = 6 Hz, 12 H), 3.9 (br s, 1 H, $w_{1/2}$ = 2.5 Hz); mass spectrum, *m*/*z* (relative intensity) 171 (2, M^+), 98 (25), 97 (83), 96 (34), 95 (29), 57 (100). The GC retention time and TLC R_f value of **24** were identical with those of **25**[15] as obtained by LAH reduction of the ketone **18**.

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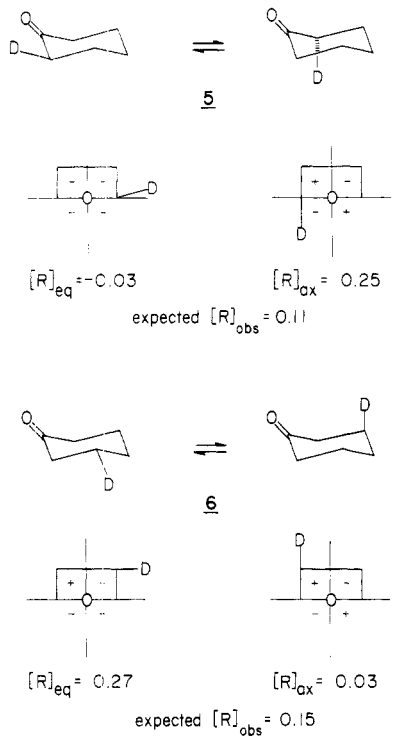
Scheme V



(1*R*,2*S*,3*R*,6*S*)-3-Methyl-6-*tert*-butyl(2-$^2H_1$)cyclohexanol (27): $[\alpha]^{25}_D$ -27.8° (*c* 0.74); ^1H NMR δ 0.98 (overlapping s and d, *J* = 6 Hz, 12 H), 3.63 (m, 1 H, $w_{1/2}$ = 23 Hz); mass spectrum, *m/z* (relative intensity) 171 (1, M^+), 98 (35) 97 (63), 96 (35), 95 (27), 82 (57), 81 (29), 57 (100), 56 (30), 55 (25). The GC retention time and TLC R_f value of **27** were identical with those of **28** as obtained by reduction of ketone **18**[15] with lithium in liquid ammonia.

(1*S*,2*R*,5*R*,6*R*)-2-Methyl-4-*tert*-butyl(6-$^2H_1$)cyclohexanol (30): $[\alpha]^{25}_D$ +36° (*c* 9.0); ^1H NMR δ 0.83 (overlapping s and d, *J* = 6 Hz, 12 H), 3.9 (br s, $w_{1/2}$ = 8.5 Hz); mass spectrum, *m/z* (relative intensity) 171 (1, M^+), 98 (42), 97 (44), 96 (52), 95 (30), 82 (31), 57 (100), 56 (38).

(3*S*,4*R*)-1-Methyl-4-*tert*-butyl(3-$^2H_1$)cyclohexene (32). To a solution of 1 g (5 mmol) of (1*S*,2*R*,4*R*,6*R*)-2-methyl-4-*tert*-butyl(6-$^2H_1$)cyclohexanol (**30**) in 10 mL of pyridine, cooled to 0 °C, was added dropwise 2 mL of phosphorus oxychloride. After being stirred for 1 h room temperature, the reaction mixture was poured onto ice and extracted with ether. The ether layer was washed with dilute hydrochloric acid, saturated bicarbonate, and water. After the mixture was dried and the solvent evaporated, 0.665 g of the olefin **32** was obtained: $[\alpha]^{25}_D$ +102° (*c* 2.7); ^1H NMR δ 0.86 (s, 12 H), 1.63 (br s, 3 H), 5.33 (br s, 1 H); mass spectrum, *m/z* (relative intensity) 153 (16, M^+), 96 (60), 95 (38), 69 (35), 68 (22), 57 (100).

(3*S*,4*R*)-4-*tert*-Butyl(3-$^2H_1$)cyclohexanone (4). A 0.493-g (3 mmol) aliquot of the olefin **32** in 1 mL of pentane was stirred under an atmosphere of HCl gas at room temperature for 8 h. At the end of this reaction period the solution was washed with saturated sodium bicarbonate and water, dried over anhydrous $MgSO_4$, and evaporated to yield 0.446 g (73%) of the chloride **34**: ^1H NMR δ 0.86 (s, 9 H), 1.76 (s, 3 H). The crude tertiary chloride **34** (0.4 g, 2 mmol) was added to a solution of potassium triethylmethoxide in triethylmethanol (prepared from 3 g of the alcohol and 0.6 g of potassium),[21] and the reaction mixture was stirred at 80 °C for 16 h, poured into water, and extracted with pentane. An analysis of the pentane solution showed the presence of two olefins, **36** and **38**, in a ratio of 5:6; 30 mg of the olefin **38** was obtained by preparative GC (10% Carbowax on Chromosorb W, 80 °C): ^1H NMR δ 0.88 (s, 9 H), 4.55 (br s, 2 H).

A 20-mg sample of the crude olefin **38** was dissolved in 2 mL of methanol and cooled to -78 °C. Ozone was passed through the solution until a faint blue color persisted, followed by the addition of 5 drops of dimethyl sulfide and stirring at room temperature for 8 h. Evaporation of the methanol and chromatography on silica gel (hexane/ether 8:2) gave ketone **3**, whose GC retention time was identical with that of authentic 4-*tert*-butylcyclohexanone: mass spectrum, *m/z* (relative intensity) 155 (8, M^+), 99 (35), 57 (100), 56 (21), 55 (20).

(3*R*,6*R*)-3-*tert*-Butyl-6-methyl(2-$^2H_1$)cyclohexene (21). To a suspension of 7 g (20 mmol) of the tosylhydrazone **19** in 250 mL of anhydrous TMEDA,[18] cooled to 0 °C, was added 120 mL of *n*-butyllithium (2 M solution in hexane). The reaction mixture was stirred at room temperature for 8 h followed by the addition of 40 mL of D_2O (Aldrich, 99.7% D_2O). The mixture was poured into water and extracted with pentane. The organic layer was washed with 5% HCl, saturated sodium bicarbonate, and water, dried over anhydrous $MgSO_4$, and evaporated to yield 2.9 g of the olefin **21**: $[\alpha]^{25}_D$ +112.3° (c 0.29); mass spectrum, *m/e* (relative intensity) 153 (3, M^+), 152 (2, M^+), 95 (25), 57 (100); isotopic content 60% d_1, 40% d_0.

(3*R*)-4-Isopropylidene(3-$^2H_1$)cyclohexanone (42). The bromo ketone **41** (1.47 g, 6 mmol)[19] was dissoved in 8 mL of pyridine and allowed to stand at room temperature for 4 days. The organic layer was washed with dilute HCl, saturated bicarbonate, and water, dried over anhydrous $MgSO_4$, and evaporated to yield 0.834 g (90%) of the ketone **42**: ^1H NMR δ 1.73 (s, 6 H); mass spectrum, *m/z* (relative intensity) 139 (95, M^+), 138 (24), 97 (87), 82 (100), 81 (49), 68 (34), 67 (36); isotopic content 73% d_1, 27% d_0.

(3*R*)-4-Isopropylidene(3-$^2H_1$)cyclohexanol (43). A solution of LAH (0.1 g) in 20 mL of anhydrous ether was added to 0.8 g (5 mmol) of the ketone **42** in 5 mL of ether. The reaction mixture was stirred at room temperature for 15 min. Upon standard workup 0.721 g (90%) of the alcohol **43** was obtained: mp 86-87 °C; ^1H NMR δ 1.66 (s, 6 H), 3.76 (m, 1 H); mass spectrum, *m/z* (relative intensity) 141 (42, M^+), 140 (13), 123 (50), 122 (31), 108 (90), 107 (57), 82 (32), 81 (26), 80 (69), 79 (72); isotopic content 73% d_1, 27% d_0.

(*R*)-($^2H_1$)Cyclohexanone (5). The toysylate **44** (1.29 g, 4 mmol) in 1 mL of anhydrous ether was added to a suspension of 1.5 g of LAH in 25 mL of anhydrous ether. After 18 h of reflux and a standard workup, GC analysis showed the presence of two compounds (**45** and **46**) in a 1:2 ratio. Separation of the olefins was achieved by GC (10% Carbowax on Chromosorb W). For olefin **45**: ^1H NMR δ 1.66 (6 H), 2.2 and 2.7 (m, 5 H), 5.6 (br s, 2 H). For olefin **46**: ^1H NMR δ 1.66 (s, 6 H).

A pentane solution of the olefin **46** (50 mg) was cooled to -78 °C and ozone passed through the solution until a faint blue color persisted. The ozonide was reduced with DMS, and the pentane solution was washed with water, dried, and evaporated. Bulb to bulb to distillation of the crude product under vacuum (~70 °C, 3 mmHg) gave pure ketone **5**: mass spectrum, *m/z* (relative inensity) 99 (1, M^+), 98 (6, M^+), 70 (31), 56 (40), 55 (100); isotopic content 73% d_1, 27% d_0.

(1*S*,3*R*)-3-Methyl(1-$^2H_1$)cyclohexane (51). To a suspension of 7 g of LAD in 500 mL of anhydrous ether was added dropwise a solution of 23 g (0.12 mol) of the mesylate **49** of (1*R*,3*R*)-3-methylcyclohexanol [**48**: $[\alpha]^{25}_D$ +83° (*c* 0.012); ^1H NMR δ 0.85 (d, *J* = 6 Hz, 3 H); 3.90 (br s, 1 H)] in 100 mL of anhydrous ether. The reaction mixture was refluxed for 24 h. Upon standard workup followed by removal of the solvent over a Vigreux column and chromatography on silver nitrate impregnated alumina with pentane as eluting solvent, 1.5 g of (1*S*,3*R*)-3-methyl($^2H_1$)cyclohexane (**51**) was obtained: mass spectrum, *m/z* (relative intensity) 99 (36, M^+), 84 (100), 57 (52), 56 (36).

(*S*)-($^2H_1$)Cyclohexanone (6). Dry ozonolysis of 1.5 g (15 mmol) of **51** by the procedure of Cohen et al.[24] yieled 1.3 g of **52** (76%), which was converted into the chloride **53** by the procedure previously described for compound **34**. Dehydrochlorination using potassium triethylmethoxide yielded a mixture of olefins **54** and **55** which was treated with ozone at -78 °C in methylene chloride until a faint blue color persisted. The ozonide was reduced with Zn/AcOH and after standard workup purified by preparative GC (10% Carbowax on Chromosorb W, 120 °C) to give **6**: mass spectrum, *m/z* (relative intensity) 99 (87, M^+), 70 (23), 69 (47), 56 (100); isotopic purity >99% d_1.

Acknowledgment. This work was supported by a grant (No. CHE 78-27413) from the National Science Foundation. We gratefully acknowledge the technical assistance

of Ms. Ruth Records. We furthermore acknowledge Dr. Craig vanAntwerp's contribution[9] to the synthesis of (S)-(3-$^2H_1$)cyclohexanone (6) and Dr. A. Kergomard (Department of Chemistry and Biology, University of Clermont, France) for providing us with the results of his work prior to publication.[27]

Registry No. 1, 68737-98-4; 2, 68687-98-9; 3, 68778-92-7; 4, 68687-91-2; 5, 75348-02-6; 6, 66529-33-7; 7, 1195-31-9; 10, 68687-94-5; 11, 68687-95-6; 12, 68678-49-9; 13, 68737-96-2; 14, 1195-31-9; 16, 68687-97-8; 18, 56782-80-0; 19, 61062-51-9; 20, 61116-80-1; 21, 68687-92-3; 22, 5856-74-6; 24, 68687-86-5; 25, 75419-01-1; 27, 68737-95-1; 28, 75419-02-2; 30, 68687-87-6; 32, 68687-88-7; 34, 68687-89-8; 36 (isomer 1), 68687-88-7; 36 (isomer 2), 75348-03-7; 38, 68687-90-1; 42, 75348-04-8; 43, 75348-05-9; 44, 75348-06-0; 45 (isomer 1), 75348-07-1; 45 (isomer 2), 75348-08-2; 46, 75365-51-4; 48, 24965-94-4; 49, 66529-34-8; 51, 66529-35-9.

Evidence against the Intramolecular Cyclization of *o*-Azidobenzenediazonium Ions

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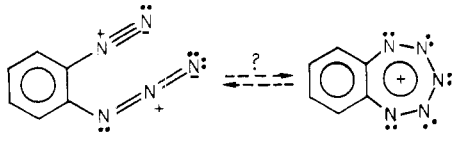
Received June 6, 1980

The question regarding the possibility that *o*-azidobenzenediazonium ions might cyclize to give pentaaza analogues of benzotropylium ions was investigated experimentally. Samples of 4-chloro-2-azidobenzenediazonium ion (**5**) and 5-chloro-2-azidobenzenediazonium ion (**6**) were prepared separately by diazotization of the corresponding chloroazidoanilines and were treated subsequently with cuprous chloride. From each of these Sandmeyer reactions only the unrearranged product was obtained: 2,5-dichloroazidobenzene from **5** and 2,4-dichloroazidobenzene from **6**. The absence of detectable amounts of crossover products in both reactions (within the limits of detection of about 5–10%) demonstrates that the conversions of ions **5** and **6** to the hypothetical benzotropylium-like cyclized ion **7** are not kinetically significant processes. The failure of this type of cyclization is attributed to a high energy barrier for the reorganization of the 12π-electron system in ions **5** and **6** to the 10π-electron system in ion **7**.

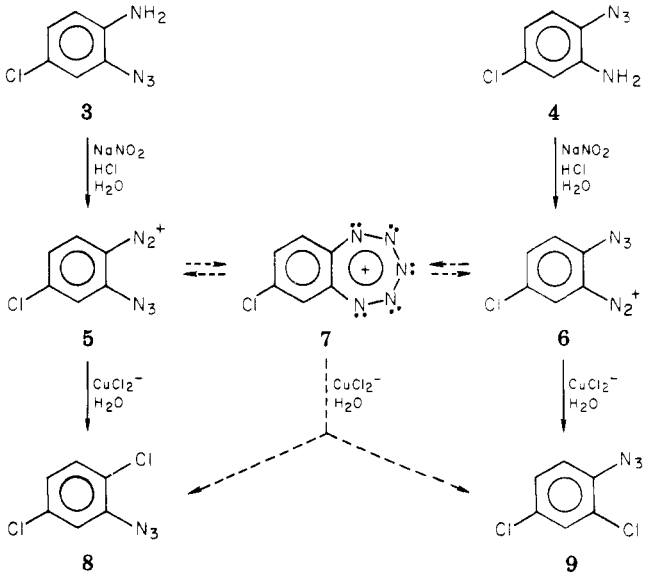
We considered the possibility that the *o*-azidobenzenediazonium ion (**1**) might cyclize to give the resonance-stabilized benzotropylium-like ion **2**. To test this idea,



1 **2**

we prepared samples of 4-chloro-2-azidoaniline (**3**) and 5-chloro-2-azidoaniline (**4**) and treated them separately with nitrous acid followed by cuprous chloride. As illustrated in Scheme I, if the azidodiazonium ions **5** and **6** fail to give the cyclized ion **7** under these conditions, then the two Sandmeyer reactions would yield different products with no crossover. Specifically, diazotization of amine **3** would generate diazonium ion **5**, which on treatment with cuprous chloride would produce exclusively 2,5-dichloroazidobenzene (**8**); diazotization of amine **4** would generate diazonium ion **6**, which on treatment with cuprous chloride would produce exclusively 2,4-dichloroazidobenzene (**9**). If, however, the azidodiazonium ions **5** and **6** equilibrate with the cyclized ion **7** under these conditions, then the same mixture of Sandmeyer products **8** and **9** would be obtained by starting either from amine **3** or from amine **4**.[2]

Scheme I



Results and Discussion

A sample of amine **3** was prepared from 4-chloro-2-nitroaniline (**10**) by the method of Hall and Patterson.[3] A sample of amine **4** was prepared analogously from 5-chloro-2-nitroaniline (**11**).[3]

(1) (a) Taken from the M.A. thesis of Donna S. Amenta, Bryn Mawr College, 1971. (b) Presented at the 168th ACS National Meeting, Atlantic City, NJ, Sept 1974; American Chemical Society: Washington, D. C., 1974; ORGN 74.

(2) In the only other studies of substituted *o*-azidobenzenediazonium ions of which we are aware, the ions (including **5**) were treated with sodium azide to synthesize the corresponding *o*-diazidobenzenes,[3] thereby precluding any information about possible crossover products.

(3) Hall, J. H.; Patterson, E. *J. Am. Chem. Soc.* **1967**, *89*, 5856–5861.

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