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α,α′-Dibromocycloalkanols and 3-Bromocycloalkene Oxides

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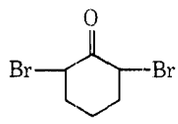
Stereoselective syntheses of the isomeric 2,6-dibromocyclohexanols and 3-bromocyclohexene oxides, as well as the related cyclooctane and cyclododecane derivatives, are reported.

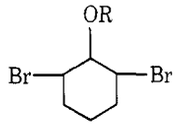
A forthcoming publication will describe our studies on the action of zinc on α,α′-dibromocycloalkanols and 3-bromocycloalkene oxides. Herein we consider the procedures by which these compounds were prepared and the evidence upon which their stereochemical assignments rest.

Results and Discussion

Dibromocyclohexanols. Bromination of cyclohexanone in acetic acid afforded *cis*-2,6-dibromocyclohexanone (**1**).[2,3] Reduction of **1** with sodium borohydride in ethanol[4] gave *cis,cis*-dibromocyclohexanol (**2**) and only a small amount of the *trans,trans*-dibromohydrin **3**. The overlapping signals for the CHBr and CHOH protons in **2** were unsuitable for structural assignments; however, the acetate derivative **2a** showed



1



2, R = H
2a, R = Ac

a triplet at 5.59 ppm (J = 2 Hz) and a multiplet at 4.09 ppm ($W_{1/2}$ = 23 Hz) which suggests the presence of an equatorial HCOAc proton and axial CHBr protons.

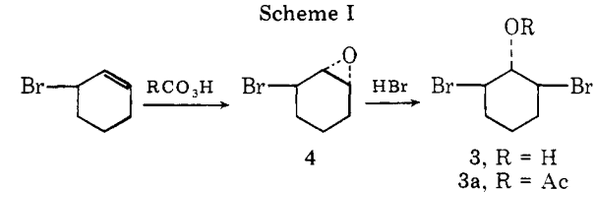
trans,trans-2,6-Dibromocyclohexanol (**3**) was obtained by the sequence shown in Scheme I. Epoxidation of 3-bromocyclohexene with *m*-chloroperbenzoic acid afforded *trans*-3-bromocyclohexene oxide (**4**).[5] The stereochemistry of **4** was assigned on the basis of the expected approach of the epoxidizing agent from the less-hindered side of the carbon–carbon double bond,[7] i.e., anti to the bromine atom. This assignment was confirmed by conversion of **4** to **3** using fuming hydrobromic acid. Dibromohydrin **3**, in turn, gave *cis*-2,6-dibromocyclohexanone (**1**) on oxidation using the Jones procedure.

The large coupling constant (J = 10.5 Hz) for the HCOAc proton in acetate **3a** placed it in an axial position. The HCBr protons must also be axial, as indicated by a complex multiplet at 3.90 ppm with $W_{1/2}$ = 31 Hz.

Although the successful reduction of substituted *trans*-2,6-dibromocyclohexanones to *cis,trans*-2,6-dibromocyclohexanols with potassium borohydride has been reported,[4] the use of sodium borohydride in the reduction of *trans*-2,6-dibromocyclohexanone (**7**) led to a mixture of *cis,cis*-dibromohydrin **2** and *cis*-3-bromocyclohexane oxide (**5**). A similar epimerization of an α-bromo ketone during sodium borohydride reduction has been noted by other investigators[8] and we have observed the same behavior in the sodium borohydride reduction of the 2,8-dibromocyclooctanones. Apparently epimerization competes with reduction when the carbonyl group is slowly reduced.

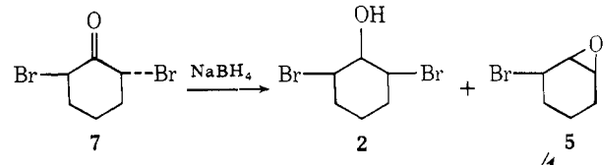
Reduction of *trans*-2,6-dibromocyclohexanone (**7**) with lithium aluminum hydride[8,9] gave a mixture of *cis,trans*-2,6-dibromocyclohexanol (**6**) and *cis*-3-bromocyclohexene oxide (**5**) as indicated by TLC and infrared examination of the crude product. Epoxide **5** was easily obtained in pure form by column chromatography, conditions under which the *cis,trans*-dibromohydrin **6** is converted into epoxide **5**. Epoxide **5** was cleanly transformed into *cis,trans*-**6** by treatment with hydrobromic acid.

Scheme I



4

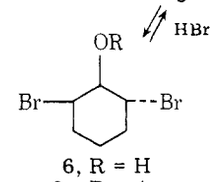
3, R = H
3a, R = Ac



7

2

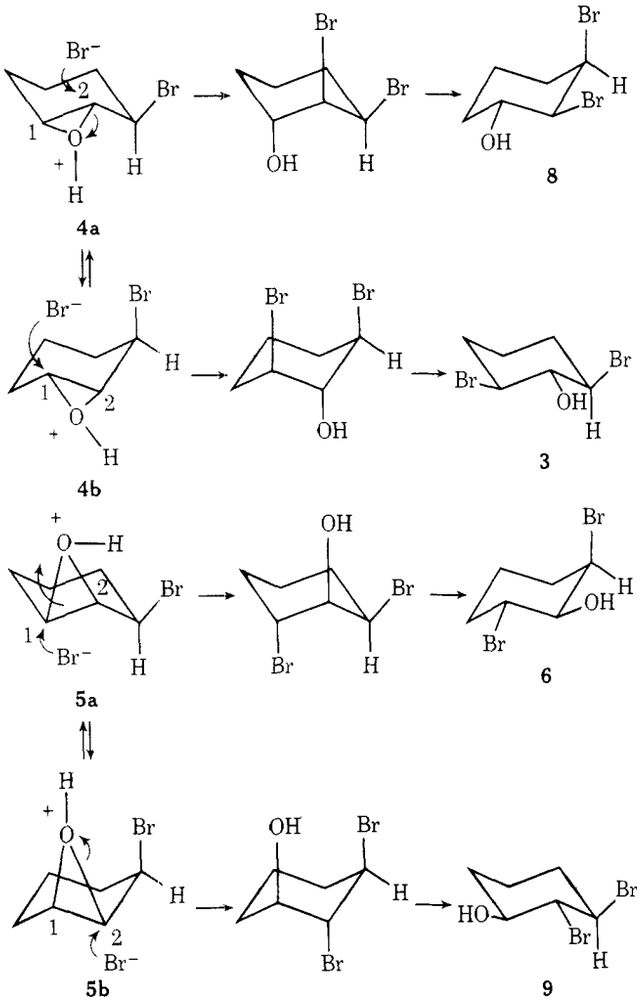
5



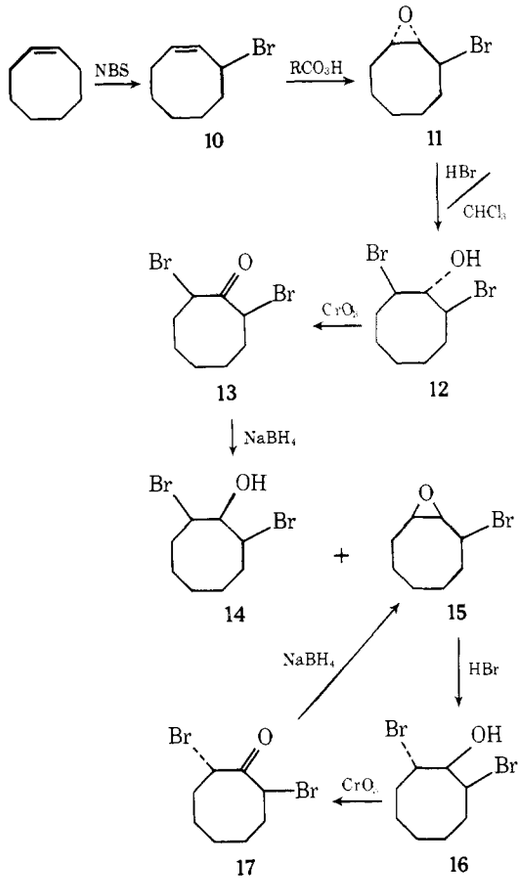
6, R = H
6a, R = Ac

0022-3263/78/1943-0875$01.00/0

Scheme II



Scheme III



cis,trans-2,6-Dibromocyclohexanol (**6**) showed three downfield multiplets, the most informative being a doublet of doublets assigned to the HCO proton which displayed $J_{1,2}$ = 8 Hz and $J_{1,6}$ = 3 Hz, requiring this proton to be axial, the C-6 proton to be equatorial, and the C-2 proton to be axial in accord with the assigned structure.

If it is assumed that acid-promoted ring opening of cyclohexene oxides proceed in a *trans*-diaxial manner, then a priori, the *trans*-oxide **4** might give dibromohydrins **3** or **8** and the *cis*-oxide **5** might afford the dibromohydrins **6** or **9**, depending upon the direction of the opening of the epoxide ring (Scheme II).

In actual fact, *trans*-bromo epoxide **4** yields dibromohydrin **3** and *cis*-bromo epoxide **5** yields dibromohydrin **6**. In each case the ring opening occurs with high stereoselectivity;[6] consequently, the transition state energies of ring opening leading to dibromohydrins **8** and **9** must be higher in energy than those leading to **3** and **6**.

It is known that bond breaking in acid-catalyzed oxide ring openings is far advanced in the transition state;[10] consequently, the stability of the intermediate carbonium ion would be expected to be reflected in the transition state energy. As the carbon–oxygen bond at C-2 begins to break in conformer **4a** or **5b**, the incipient positive charge at C-2 is destabilized by the inductive effect of the adjacent bromine atom. This would raise the transition state energy of the ring opening at C-2.

On the other hand, potential 1,3-diaxial interactions in transition **4b** leading ultimately to dibromohydrin **3** would be expected to deter ring cleavage at C-1. Evidently the inductive effect of the electronegative bromine atom is the controlling factor in the ring opening. Bannard has come to a similar conclusion regarding the acid-promoted ring openings of *cis*- and *trans*-3-methoxycyclohexene oxides,[11] while Needler[12] has observed the formation of *trans,trans*-2-chlorocyclohexanol derivatives in the ring opening of *trans*-3-chlorocyclohexene oxide.

2,8-Dibromocyclooctanols. The three 2,8-dibromocyclooctanols were obtained, as outlined in Scheme III, using reactions which parallel those employed in the six-membered series.

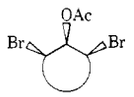
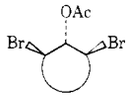
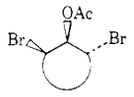
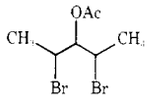
Epoxidation of 3-bromocyclooctene (**10**) gave *trans*-3-bromocyclooctene oxide (**11**), which was converted to *trans,trans*-2,8-dibromocyclooctanol (**12**) by treatment with hydrobromic acid. Oxidation of **12** using the Jones procedure afforded *cis*-2,8-dibromocyclooctanone (**13**).

Sodium borohydride reduction of *cis*-2,8-dibromocyclooctanone (**13**) afforded a mixture of *cis*-3-bromocyclooctene oxide (**15**) and *cis,cis*-2,8-dibromocyclooctanol (**14**) in a ratio of 3:1. Sodium borohydride reduction of *trans*-dibromide **17** gave the *cis*-bromo epoxide **15** and a small amount of *cis,cis*-dibromohydrin **14**. It is apparent that epimerization of the dibromocyclooctanones competes with the slow reduction of the carbonyl group and that reduction of *trans*-dibromide **17** leads to epoxide **15**, whereas reduction of the *cis*-dibromide **13** affords the *cis,cis*-dibromohydrin **14**.

The last stereoisomer in this series, *cis,trans*-2,8-dibromocyclooctanol (**16**), was obtained by treating a solution of *cis*-bromo epoxide **15** in chloroform with hydrobromic acid.

The structures assigned compounds **11**–**17** are based on their method of preparation, analysis of NMR spectra, and further chemical transformations. The *cis,cis*-dibromohydrin **14** was the only isomer which could be chromatographed on acid-washed alumina. Chromatography of *trans,trans*-**12** and *cis,trans*-**16** cleanly gave *trans*-bromo epoxide **11** and *cis*-bromo epoxide **15**, respectively.

Table I. NMR Spectra of 6-, 8-, and 12-Membered Ring Dibromo Acetates and 2,4-Dibromo-3-pentyl Acetate

	Compd	—CHBr	—CHOAc
	C_6	4.09	5.59 (t, J = 2 Hz)
	C_8	4.41 (m)	5.85 (t, J = 2 Hz)
	C_{12}	4.23 ("q")	5.55 (t, J = 5 Hz)
	C_6	3.90 (m)	5.33 (t, J = 10.5 Hz)
	C_8	4.25 (m)	5.43 (t, J = 9.5 Hz)
	C_{12}	4.26 ("q")	5.27 (t, J = 5 Hz)
	C_6	4.70 (m)	4.88 (d of d, J = 3,
		4.32 (m)	8 Hz
	C_8	4.37 (m)	5.22 (d of d, J = 9.5, 2 Hz)
	C_{12}	4.25 (m)	5.62 (d of d, J = 10.3, 1.8 Hz)
 *dl*		4.31 (m)	5.02 (t, J = 5.5 Hz)

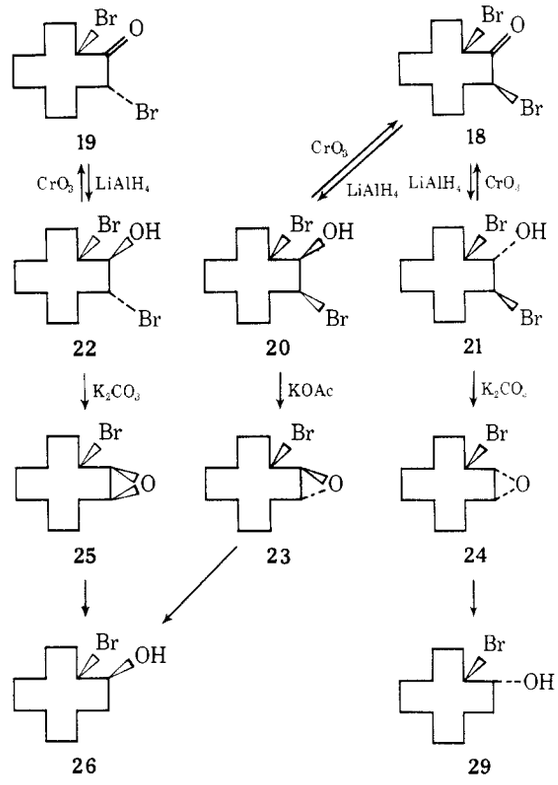
The cyclooctane ring is known to adopt a number of low energy conformations[13] in which C-1, C-2, C-3, C-7, and C-8 atoms take up positions resembling the chair conformation of a cyclohexane ring. Examination of Table I demonstrates a close parallel between the multiplicities and spin coupling constants of the HCBr and HCO protons in the related six- and eight-membered ring isomers, adding additional support for the geometric assignments made in the cyclooctane series.

Dibromocyclododecanols. The dibromohydrins in the 12-membered ring series were prepared by a modification of Garbisch's procedure.[14] Bromination of cyclododecanone in ether afforded a 7:3 mixture of *cis*- and *trans*-2,12-dibromocyclododecanones from which the pure *cis*-**18** and *trans*-**19** could be obtained by fractional crystallization. Lithium aluminum hydride reduction of *cis*-**18** gave *cis,cis*-2,12-dibromocyclododecanol (**20**) and *trans,trans*-2,12-dibromocyclododecanol (**21**),[15] which were separated by chromatography (Scheme IV). Reduction of *trans*-dibromocyclododecanone **19** afforded a single alcohol, *cis,trans*-2,12-dibromocyclododecanol (**22**), confirming the trans relationship of the two bromine atoms in the parent ketone. Jones oxidation of each dibromohydrin gave only the original parent dibromo ketone, demonstrating the absence of epimerization during hydride reduction.

cis,cis-Dibromohydrin **20** was readily converted to *cis*-3-bromo-*trans*-1,2-epoxycyclododecane (**23**) by treatment with potassium acetate in acetone. These conditions had no effect on *trans,trans*-dibromohydrin **21** or *cis,trans*-dibromohydrin **22** and the more basic potassium carbonate in aqueous methanol was required to produce *trans*-3-bromo-*cis*-1,2-epoxycyclododecane (**24**) and *cis*-3-bromo-*cis*-1,2-epoxycyclododecane (**25**), respectively. Only one of the two possible epoxides was formed from *cis,trans*-dibromohydrin **22** and the structure **24** was assigned on the basis of evidence to be discussed later. A mixture of epoxides **23**, **24**, and **25** was obtained on epoxidation of 3-bromocyclododecene; once again we failed to observe the formation of the fourth bromo epoxide.

Chemical transformations were required to differentiate between *cis,cis*-dibromohydrin **20** and *trans,trans*-dibromohydrin **21**, since NMR spectral data, unlike the situation in the six- and eight-membered rings, gave no clue to their identity (See Table I). The cis,cis configuration was assigned to **20** on the basis of its reduction with lithium aluminum hydride to *cis*-2-bromocyclododecanol (**26**), which was also

Scheme IV

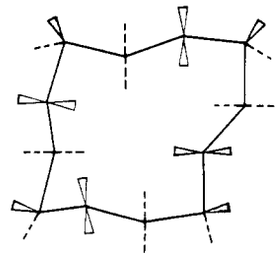


prepared from *trans*-cyclodecene oxide (**27**) and hydrobromic acid. Additional support for the cis,cis configuration was provided by the formation of *cis*-bromohydrin **26** on lithium aluminum hydride reduction of *cis*-bromo *trans*-epoxide **23**.

Lithium aluminum hydride reduction of *trans,trans*-dibromohydrin **21** gave a mixture of starting dibromohydrin **21**, cyclododecanol (**28**), and 7% of *trans*-2-bromocyclododecanol (**29**). Apparently, the reduction of **29** to cyclododecanol (**28**) occurs faster than the initial reduction of dibromohydrin **21**. Lithium aluminum hydride reduction of *trans*-bromo *cis*-epoxide **24** afforded *trans*-bromohydrin **29** in 75% yield.

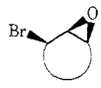
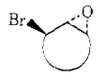
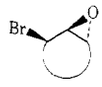
Finally, lithium aluminum hydride reduction of the epoxide derived from *cis,trans*-dibromohydrin **22** gave, in addition to recovered epoxide and 2-cyclodecenol, a low yield of *cis*-2-bromocyclododecanol (**26**), which suggests the epoxide has the constitution represented by structure **25**.

Evidence has accumulated indicating the cyclododecane ring assumes a square conformation[16] of D_{4h} symmetry in which each side is composed of a butane segment with the corner atoms common to two segments. This arrangement permits a completely staggered conformation for each carbon atom.



The coupling constants observed for *cis*-2-bromocyclododecanol (**26**) and its acetate derivative (J = 2.0 and 1.6 Hz) and *trans*-2-bromocyclododecanol (**29**) (J = 7.0 and 7.3 Hz) suggest that the cyclododecane ring adopts a square shape with the large groups pointing outward and at least one of the

Table II. NMR Spectra of 3-Bromocycloakene Oxides

	CHBr	CH—CH
	C_6 4.43 (d of t) C_8 4.59 (m) C_{12} 3.63 (m)	3.38 (d) 3.20 (m) 3.06 (m) and 2.92 (m)
	C_6 4.52 (m) C_8 3.81 (m) C_{12} 3.92 (m)	3.28 (m) 3.07 and 2.91 (br d's) 3.21 (m) and 3.07 (m)
	C_{12} 4.64 (m)	3.10 (d of t) 2.72 (t)

groups attached to a corner carbon. In this conformation the trans isomer has a large dihedral angle (~170°) between vicinal hydrogens and should give rise to a large coupling constant, whereas the dihedral angle in the cis isomer is close to 60° and it would be expected to show a small coupling constant in accord with the experimental observations. Arranging the large groups along the "side" of the square would predict just the opposite dihedral angles for the cis and trans isomers and would require the cis isomer to have a large group facing into the ring.

In the case of the dibromohydrins or their acetate derivatives it seems reasonable to assume the most stable conformation of the cyclododecane ring would involve a "square" with the large groups pointing away from the ring. Two interconvertible conformations can be envisioned, a symmetric one where the acetate group occupies a corner and is flanked by bromine atoms, and an unsymmetric conformation in which a bromine atom is at a corner and the acetate and second bromine atom are at side positions. The symmetric conformation correctly predicts the relative HCOAc chemical shift and the unequal HCBr–CHOAc coupling constants (J_{AX} = 10.3 and J_{BX} = 1.8 Hz) displayed by the acetate derivative of *cis,trans*-2,12-dibromocyclododecanol (**22**).

The acetate derivatives derived from the *cis,cis*- and *trans,trans*-dibromohydrins both exhibit vicinal coupling constants equal to 5 Hz, which is almost identical with that displayed by the open-chain analogue *dl*-2,4-dibromo-3-pentyl acetate (**31**). Neither the symmetric nor unsymmetric conformation described above predicts this value and suggests that even with three large groups, *cis,cis*-**20** and *trans,trans*-**21** are sufficiently mobile to attain an average conformation comparable with that of an open-chain analogue.

Finally, mention is made of the upfield chemical shift for the –CHBr proton in bromo expoxides **24** and **25** and *trans*-3-bromocyclooctene oxide (**11**) (see Table II) which demands conformations for these compounds where the CHBr proton lies above and in the shielding cone of the epoxide ring.[17] Examination of the cyclododecane square model suggests that if one of the oxygen atoms of a *cis*-epoxide is located at a "corner", the CHBr proton will extend over the epoxide ring and result in an upfield shift, whereas, with a *trans*-epoxide ring the CHBr proton is directed away from the epoxide ring and would be expected to exhibit a normal chemical shift. Examination of molecular models of *cis*- and *trans*-bromocyclooctene oxides **11** and **15** likewise illustrate that the CHBr proton can only be positioned over the epoxide ring in the trans isomer **11**.

Experimental Section

All boiling and melting points are uncorrected. Infrared spectra were measured with a Perkin-Elmer Infracord Model 137-B. NMR spectra were recorded with Varian Associates A-60A and Perkin-Elmer R-32 instruments and are reported in parts per million from tetramethylsilane as an internal standard. Mass spectra were determined on a Hitachi RMU-6D instrument by the Purdue University Spectral Service. Microanalyses were performed by Dr. C. S. Yeh and associates.

***cis,cis*-2,6-Dibromocyclohexanol (2).** To 3.5 g of *cis*-2,6-dibromocyclohexanone (**1**)[2] in 30 mL of absolute ethanol at 5 °C was added dropwise a solution of 800 mg of sodium borohydride in 80 mL of ethanol. The mixture was allowed to stir for 5 h at 5 °C and 30 h at ambient temperature. The mixture was diluted with water, neutralized to pH 7 with 5% hydrochloric acid, and extracted with ether. The ether layer was dried ($MgSO_4$) and evaporated to leave a light green oil which solidified on cooling. Recrystallization from hexane gave 1.56 g (45%) of **2**: mp 60–62 °C; IR (CCl_4) 2.69 μm; NMR (CCl_4) 1.0–2.3 (m, 6, $-CH_2-$), 2.5 (d, 1, J = 3 Hz, –CHO**H**), and 3.9 ppm (m, 3, –CHO and CHBr).

Anal. Calcd for $C_6H_{10}Br_2O$: C, 27.91; H, 3.87; Br, 62.01. Found: C, 28.16; H, 4.02; Br, 61.85.

***cis,cis*-2,6-Dibromocyclohexyl Acetate (2a).** A mixture of 150 mg of **2**, 500 mg of powdered magnesium, and 5 mL of acetyl chloride was stirred for 38 h at ambient temperature. The solution was decanted and the solids washed thoroughly with ether. Water was added slowly to the combined supernatant and ether washings. The ether solution was then washed with 5% sodium bicarbonate solution, dried, and concentrated to afford 140 mg of solid which was recrystallized from hexane and showed: mp 76–78 °C; IR ($CHCl_3$) 5.79 μm; NMR ($CDCl_3$) 1.6–2.1 (m, 6, $-CH_2-$), 2.13 (s, 3, CH_3CO_2-), 4.09 (m, 2, $W_{1/2}$ = 23 Hz, –CHBr), and 5.59 ppm (t, 1, J = 2 Hz, –CHOAc); mass spectrum (70 eV) m/e 256[18] (P – 42), 238 (P – 60), 219 (P – Br), and 159 (P – 60 – Br).

Anal. Calcd for $C_8H_{12}Br_2O_2$: C, 32.00; H, 4.00; Br, 53.33. Found: C, 32.21; H, 3.85; Br, 53.35.

***trans*-3-Bromocyclohexene Oxide (4).** To 8.35 g (0.052 mol) of 3-bromocyclohexene[19] in 40 mL of chloroform at ice-bath temperature was added over a 15-min period a solution of 15.0 g of 85% *m*-chloroperbenzoic acid in 200 mL of chloroform. The mixture was stirred at ambient temperature for 30 h, filtered, washed with 10% sodium sulfite solution and 5% sodium bicarbonate solution, dried, concentrated, and distilled under diminished pressure to give 5.09 g of oxide **4**: bp 64–68 °C (4 mm); $n^{20}D$ 1.5151–1.5158; IR (CCl_4) 8.00, 8.48, 9.89, and 10.31 μm; NMR (CCl_4) 1.1–2.2 (m, 6, $-CH_2-$), 3.28 (m, 2, c-CHCHO), and 4.52 ppm (m, 1, –CHBr).

Anal. Calcd for C_6H_9BrO: C, 40.68; H, 5.08; Br, 45.20. Found: C, 40.65; H, 4.98; Br, 45.40.

***trans,trans*-2,6-Dibromocyclohexanol (3).** A mixture of 734 mg of oxide **4** in 10 mL of chloroform and 10 mL of fuming hydrobromic acid was stirred vigorously for 70 min. The layers were separated and the aqueous phase was washed with chloroform. The combined chloroform layers were washed with 10% aqueous sodium carbonate, dried, and concentrated to furnish 783 mg of white solid. The analytical sample of **3** was obtained by recrystallization from hexane: mp 93–95 °C; IR ($CHCl_3$) 2.74 μm; NMR ($CDCl_3$) 1.1–2.6 (m, 6, $-CH_2-$), 3.0 (s, 1, –OH), and 3.88 ppm (m, 3, –CHO, –CHBr); mass spectrum m/e 256 (P), 238 (P – 18), 177 (P – Br), 159 (P – 18 – Br).

Anal. Calcd for $C_6H_{10}Br_2O$: C, 27.91; H, 3.87; Br, 62.01. Found: C, 27.85; H, 3.85; Br, 62.18.

A solution of 102 mg of **3** in 4 mL of acetone at 40 °C was treated with 3.1 mL of Jones reagent. The usual workup after 30 min gave 73 mg of solid whose IR spectrum indicated the presence of some unreacted alcohol. This material was again treated with Jones reagent and workup gave 50 mg of solid. Recrystallization from hexane gave a solid, mp 106–108 °C, whose infrared spectrum was identical with that of an authentic sample of *cis*-2,6-dibromocyclohexanone (**1**).

***trans,trans*-2,6-Dibromocyclohexyl Acetate (3a).** Using the procedure described earlier, 183 mg of **3** afforded 176 mg of **3a**. The analytical sample was prepared by crystallization from hexane: mp 113–115 °C; IR ($CHCl_3$) 5.81 μm; NMR ($CDCl_3$) 1.4–2.7 (m, 6, $-CH_2-$), 2.19 (s, 3, CH_3CO_2-), 3.90 (m, 2, $W_{1/2}$ = 31 Hz, –CHBr) and 5.33 ppm (t, 1, J = 10.5 Hz, –CHOAc); mass spectrum m/e 256 (P – 42), 238 (P – 60), 219 (P – Br), 159 (P – 60 – Br).

Anal. Calcd for $C_8H_{12}Br_2O_2$: C, 32.00; H, 4.00; Br, 53.33. Found: C, 32.16; H, 4.04; Br, 53.23.

***cis,trans*-2,6-Dibromocyclohexanol (6).** To 1.69 g (6.6 mmol) of *trans*-2,6-dibromocyclohexanone (**7**)[2,3] in 50 mL of ether was added 85 mg (2.24 mmol) of lithium aluminum hydride. The reaction mixture was stirred for 20 min and then worked up to afford 955 mg of colorless oil. The analytical sample was obtained by evaporative distillation [55 °C (0.05 mm)]: IR 2.86 μm; NMR ($CDCl_3$) 1.5–2.6 (m, 6, $-CH_2-$), 3.05 (s, 1, –OH), 3.72 (d of d, 1, $J_{1,2}$ = 8, $J_{1,6}$ = 3 Hz, HCO), 4.35 (m, 1, –CHBr), and 4.75 ppm (m, 1, –CHBr); mass spectrum m/e 260 (P) and 179 (P – Br).

Anal. Calcd for $C_6H_{10}Br_2O$: C, 27.91; H, 3.91. Found: C, 27.90; H, 4.11.

Oxidation of **6** employing the Jones procedure afforded a solid, mp 33–35 °C, whose IR and NMR were identical with those of authentic *trans*-2,6-dibromocyclohexanone (**7**).

The acetate derivative of **6** could not be induced to crystallize: NMR (CCl_4) 1.6–2.5 (m, 6, $-CH_2-$), 2.10 (s, 3, CH_3CO_2), 4.32 (m, 1, $W_{1/2}$ = 27 Hz, –CHBr), 4.70 (m, 1, $W_{1/2}$ = 15 Hz, –CHBr), and 4.88 ppm (d of d, 1, J = 8, 3 Hz, –CHOAc); mass spectrum *m/e* 256 (P − 42), 238 (P − 60), 219 (P − Br), and 159 (P − 60 − Br).

***cis*-3-Bromocyclohexene Oxide (5).** A 0.415 g sample of *cis,trans*-2,6-dibromocyclohexanol (**6**) was placed on 18 g of acid-washed alumina and was eluted with 5–10% ether in pentane to give 0.25 g (87%) of *cis*-bromo epoxide **5**. The analytical sample of **5** was prepared by evaporative distillation [51–55 °C (0.17 mm)]: IR 10.63 and 12.58 μm; NMR 1.0–2.18 (m, 6, $-CH_2-$), 3.38 (m, 2, c-CHCHO), and 4.43 ppm (d of t, 1, –CHBr); mass spectrum (70 eV) *m/e* (rel intensity) 177 (0.68), 175 (0.57), 97 (100), 79 (27), 67 (29), 43 (23), 39 (57).

Anal. Calcd for C_6H_9BrO: C, 40.71; H, 5.12. Found: C, 40.71; H, 5.26.

A mixture of 0.50 g of epoxide **5** in 10 mL of $CHCl_3$ and 10 mL of 47% hydrobromic acid was stirred for 70 min. The usual workup left 0.55 g of an oil whose infrared spectrum was identical with that of *cis,trans*-**6** and whose NMR spectrum only displayed signals shown by alcohol **6**.

Sodium Borohydride Reduction of *trans*-2,6-Dibromocyclohexanone (7). To 1.6 g of *trans*-2,6-dibromocyclohexanone (**7**) in 50 mL of absolute ethanol at 0 °C was added a solution of 236 mg of sodium borohydride in 40 mL of absolute ethanol. The mixture was stirred for 5 h and worked up to leave 1.02 g of yellow oil. Thin layer chromatography indicated the presence of a mixture of *cis,cis*-2,6-dibromocyclohexanol (**2**) and *cis*-3-bromocyclohexene oxide (**5**).

This mixture was treated in chloroform with fuming hydrobromic acid and after workup and chromatography on silica gel gave 310 mg of a mixture which was free of a small amount of carbonyl impurity present in the crude product.

A small portion (40 mg) of the chromatographed product was treated with acetyl chloride and magnesium to afford a mixture of acetates **2a** and **6a**, which were identified by TLC comparison with authentic samples. Integration of the triplet at 5.69 ppm and doublet of doublets at 5.00 ppm suggested **2a** and **6a** were present in a ratio of 3:5.

***trans*-3-Bromocyclooctene Oxide (11).** To a solution of 25.6 g (0.135 mol) of 3-bromocyclooctene[20] in 50 mL of chloroform at 5 °C was added dropwise a solution of 29.3 g (0.156 mol) of 85% *m*-chloroperbenzoic acid in 300 mL of chloroform. After stirring at room temperature for 18 h, workup and distillation gave 22.3 g (80%) of epoxide **11**: bp 64–68 °C (0.2 mm); $n^{23}D$ 1.5224; NMR (CCl_4) 1.8–2.1 (m, 10, $-CH_2-$), 2.91 (br d, 1, c-CCHO), 3.07 (br d, 1, c-CHCO), and 3.81 ppm (m, 1, $W_{1/2}$ = 25 Hz, –CHBr); mass spectrum *m/e* 159 (P − 45) and 125 (P − Br).

Anal. Calcd for $C_8H_{13}OBr$: C, 46.82; H, 6.34; Br, 39.02. Found: C, 46.70; H, 6.20; Br, 39.22.

***trans,trans*-2,3-Dibromocyclooctanol (12).** A mixture of 15 mL of fuming hydrobromic acid and a solution of 2.43 g of epoxide **11** in 30 mL of chloroform was stirred vigorously at ambient temperature for 12 h. The usual workup gave 2.75 g of oil which gradually solidified. Two recrystallizations from hexane afforded 637 mg of pure **12**: mp 62–64 °C; IR (CCl_4) 2.73 μm; NMR (CCl_4) 1.72 (m, 6, $-CH_2-$), 2.35 (m, 4, $-CH_2CBr$), 3.03 (s, 1, –OH), and 4.28 ppm (m, 3, –CHOH, –CHBr).

Anal. Calcd for $C_8H_{14}OBr_2$: C, 33.57; H, 4.89; Br, 55.94. Found: C, 33.34; H, 4.97; Br, 55.88.

***trans,trans*-2,8-Dibromocyclooctyl acetate** was prepared from **12** by stirring with magnesium and acetyl chloride and was purified by recrystallization from hexane: mp 82–83 °C; NMR (CCl_4) 2.08 (s, 3, CH_3CO_2-), 1.78 (m, 6, $-CH_2-$), 2.3 (m, 4), 4.25 (m, 2, $W_{1/2}$ = 25 Hz, –CHBr), and 5.43 ppm (t, 1, J = 9.5 Hz, –CHOAc).

Anal. Calcd for $C_{10}H_{16}Br_2O_2$: C, 36.59; H, 4.88; Br, 48.76. Found: C, 36.81; H, 4.92; Br, 48.77.

***cis*-2,8-Dibromocyclooctanone (13).** To a solution of 362 mg of *trans,trans*-2,8-dibromocyclooctanol (**12**) in 25 mL of pure acetone at 10 °C was slowly added a solution containing 309 mg of chromium trioxide and 0.30 mL of concentrated sulfuric acid in 2 mL of water. The usual workup of the reaction mixture gave 283 mg of **13**. The analytical sample of **13** was prepared by recrystallization from hexane and showed: mp 93.5–95.5 °C; IR (CCl_4) 5.72 μm; NMR ($CDCl_3$) 1.0–2.71 (m, 10, $-CH_2-$) and 4.91 ppm (d of d, 2, $W_{1/2}$ = 13.5 Hz, –CHBr).

Anal. Calcd for $C_8H_{12}Br_2O$: C, 33.80; H, 4.22; Br, 56.34. Found: C, 33.54; H, 4.37; Br, 56.24.

Sodium Borohydride Reduction of *cis*-2,8-Dibromocyclooctanone (13). A solution of 2.3 g (8.1 mmol) of *cis*-2,8-dibromocyclooctanone (**13**) and 0.31 g (8.1 mmol) of sodium borohydride in 50 mL of absolute ethanol was stirred at ambient temperature for 86 h. The mixture was worked up to give 1.7 g of an oil which was chromatographed on 110 g of Florisil using 2% ether–hexane as an eluant. The first component to be eluted, 790 mg, was *cis,cis*-2,8-dibromocyclooctanol (**14**): mp 54–54.2 °C; IR (CCl_4) 2.72 μm; NMR (CCl_4) 1.2–2.8 (m, 10), 2.68 (d, 1, J = 4 Hz, –OH), 4.38 (m, 2, $W_{1/2}$ = 21 Hz, –CHBr), and 4.69 ppm (m, 1, –CHO). The 2.68-ppm doublet disappeared when trifluoroacetic acid was added and the signal at 4.69 ppm collapsed to a triplet, J = 2 Hz.

Anal. Calcd for $C_8H_{14}Br_2O$: C, 33.57; H, 4.89; Br, 55.94. Found: C, 33.76; H, 4.79; Br, 55.74.

The later chromatographic fractions containing **14** (140 mg) were contaminated with *cis*-3-bromocyclooctene oxide (**15**). Evaporative distillation of these fractions gave 60 mg of **14** and 80 mg of **15**.

The last chromatographic fractions gave **15**. A pure sample of epoxide **15** was obtained by evaporative distillation; NMR (CCl_4) 1.2–2.5 (m, 10), 3.20 (m, c-CHCHO), and 4.59 ppm (m, 1, $W_{1/2}$ = 22 Hz, –CHBr).

Anal. Calcd for $C_8H_{13}BrO$: C, 46.82; H, 6.34; Br, 39.02. Found: C, 46.61; H, 6.28; Br, 39.19.

Sodium Borohydride Reduction of *trans*-2,8-Dibromocyclooctanone (17). A solution of 730 mg (19.2 mmol) of sodium borohydride in 90 mL of absolute ethanol was slowly added to a solution of 3.4 g (11.9 mmol) of *trans*-2,8-dibromocyclooctanone (**17**)[21] (mp 75.5–77.5 °C) in 100 mL of absolute ethanol and the mixture was stirred at ambient temperature for 18 h. The usual workup gave 1.4 g of oil which was chromatographed on 80 g of Florisil using 1% ether–hexane as an eluant to furnish 919 mg of *cis*-3-bromocyclooctene oxide (**15**). The first fractions of **15** were contaminated with *cis,cis*-2,8-dibromooctanol (**14**). The epoxide **15** was separated by evaporative distillation at 50 °C and 5 mm. The residue from distillation (57 mg) was recrystallized from hexane, mp 55–56 °C, and showed an IR spectrum identical with that of cis,cis alcohol **14**.

***cis,trans*-2,8-Dibromocyclooctanol (16).** A solution of 853 mg of *cis*-3-bromocyclooctene oxide (**15**) in 10 mL of chloroform was stirred vigorously at ambient temperature with 2 mL of fuming hydrobromic acid. The organic layer was separated and washed with 5% sodium bicarbonate solution, dried, and concentrated to yield 1.01 g of oil. Column chromatography using 80 g of Florisil and 10–50% benzene–hexane as eluant gave 800 mg of cis,trans alcohol **16**. A pure sample of **16** was obtained by evaporative distillation at 80 °C and 0.2 mm: IR 2.73 μm; NMR (CCl_4) 1.4–2.5 (m, 10, $-CH_2-$), 2.79 (s, 1, –OH), 4.0–4.8 (m, 3, –CHO and –CHBr); mass spectrum *m/e* 288 (P), and 270 (P − 18).

The use of Florisil as the support for the chromatographic purification was necessitated by the fact that silica gel and basic alumina appeared to react with the alcohols, while acid-washed alumina converted cis,trans alcohol **16** and trans,trans alcohol **12** into bromo epoxides **15** and **11**, respectively. Thus 395 mg of crude *cis,trans*-dibromo alcohol **16** on chromatography using acid-washed alumina gave 280 mg of bromo epoxide **15** as the only recoverable product. Similarly, chromatography of 228 mg of *trans,trans*-dibromo alcohol **12** on acid-washed alumina and elution with 60% hexane–ether gave 156 mg of bromo epoxide **11**. *cis cis*-Dibromo alcohol **14** was recovered unchanged from chromatography under these conditions.

***cis,trans*-2,8-Dibromocyclooctyl Acetate (16a).** Acetylation of **16** using magnesium and acetyl chloride gave oily acetate **16a**: NMR 1.6–2.0 (m, 6, $-CH_2-$), 2.09 (s, 3, CH_3CO-), 2.0–2.7 (m, 4, $-CH_2CBr$) 4.37 (m, 2, $W_{1/2}$ = 25 Hz, –CHBr), 5.22 (d of d, 1, J = 9.5, 2 Hz, –CHOAc).

Epimerization of *trans*-2,8-Dibromocyclooctanone (17). To 70 mL of absolute ethanol was added 23 mg of sodium and 2.09 g of *trans*-2,8-dibromocyclooctanone (**17**). Aliquots (5 mL) were removed at various time intervals and were diluted with water and extracted with ether. The organic phase was separated, dried, and evaporated and the resulting solid analyzed by NMR. The *trans*-dibromide showed an apparent triplet centered at 4.63 ppm, whereas the *cis*-dibromide (**13**) displayed a quartet centered at 4.92 ppm. In 1 h the *trans/cis* ratio was 5.6:1. After 13 h it reached 4.3:1 and did not change afterwards (82 h).

***cis,trans*-2,12-Dibromocyclododecanol (22).** To an ethereal solution of 5.01 g (0.0147 mol) of *trans*-2,12-dibromocyclododecanone (**19**),[14] mp 44–45 °C, was added 0.579 g (0.0152 mol) of lithium aluminum hydride and the mixture was stirred for 3 h at ambient temperature. Workup led to the isolation of 4.28 g of oil which crystallized

on standing. Recrystallization from ether afforded 3.28 g (65%) of *cis,trans*-**22**: mp 73–75 °C (lit.[14] 76 °C); NMR ($CDCl_3$) 1.35 and 1.94 (s and m, 18), 2.87 (s, 1, –OH), 4.15 (m, 2, $W_{1/2}$ = 11 Hz), and 4.42 ppm (m, 1, $W_{1/2}$ = 18 Hz); IR ($CHCl_3$) 2.78 μm.

Oxidation of **22** according to the Jones procedure occurred rapidly and afforded 67% of a solid whose melting point and NMR spectrum were identical with that of *trans*-2,12-dibromocyclododecanone (**19**).

cis,trans-2,12-Dibromocyclododecyl acetate (**22a**) was prepared in 85% yield by acetylation of **22** with acetyl chloride in the presence of magnesium powder and showed: mp 90–95 °C; IR ($CHCl_3$) 5.70 μm; NMR ($CDCl_3$) 1.38 and 1.96 (s and m, 18), 2.17 (s, 3, CH_3CO_2–), 4.25 (m, 2, –CHBr) and 5.62 (d or d, 1, J = 10.3, 1.8 Hz, –CHOAc).

***cis,cis*- and *trans,trans*-2,12-Dibromocyclododecanol (20 and 21).** To an ether solution of 8.25 g (0.243 mol) of *cis*-2,12-dibromocyclododecanone (**18**),[14] mp 123–125 °C, was slowly added 0.7 g (0.0184 mol) of lithium aluminum hydride. The mixture was stirred at ambient temperature for 8 h and worked up to give 7.20 g of oil. Chromatography of 4.371 g of the oil on 100 g of silica gel using 5% ether–pentane as an eluant yielded 2.16 g of pure *cis,cis*-**20** followed by 1.23 g of pure *trans,trans*-**21**.

cis,cis-2,12-Dibromocyclododecanol (**20**) showed: mp 37–38 °C (lit.[14] mp 40 °C); IR ($CDCl_3$) 2.76 μm; NMR ($CDCl_3$) 1.38 and 2.05 (s and m, 18), 2.82 (m, 1, –OH), and 4.32 ppm (m, 3, CHBr and –CHO–).

trans,trans-2,12-Dibromocyclododecanol (**21**) proved to be an oil and could not be induced to crystallize:[15] IR ($CHCl_3$) 2.81 μm; NMR ($CDCl_3$) 1.4 and 2.0 (s and m, 18), 2.60 (s, 1, –OH), 3.78 ("t", 1, J = 5 Hz, –CHO–), and 4.32 ppm ("q", 2, J = 5 Hz, –CHBr).

Oxidation of **20** and **21** using the Jones procedure afforded *cis*-2,12-dibromocyclododecanone (**18**) in yields of 65 and 80%, respectively.

cis,cis-2,12-Dibromocyclododecyl acetate (**20a**) was obtained in 90% yield from the reaction of **20** with acetyl chloride and magnesium powder and exhibited: IR 5.68 μm; NMR ($CDCl_3$) 1.32 and 1.90 (s and m, 18), 2.10 (s, 3, CH_3CO_2–), 4.23 ("q", 2, –CHBr), and 5.55 ppm (t, 1, J = 5 Hz, –CHOAc).

trans,trans-2,12-Dibromocyclododecyl acetate (**21a**) was prepared in 93% yield by the same procedure and showed: IR 5.70 μm; NMR ($CDCl_3$) 1.32 and 1.90 (s and m, 18), 2.09 (s, 3, CH_3CO_2–), 4.26 ("q", 2, –CHBr), and 5.27 ppm (t, 1, J = 5 Hz, –CHOAc).

***cis*-3-Bromo-*cis*-1,2-epoxycyclodecane (25).** To a solution of 2.36 g (6.91 mmol) of *cis,trans*-**22** in 50 mL of methanol was added 2.0 g (14.5 mmol) of potassium carbonate in 10 mL of methanol and 1 mL of water. The mixture was stirred for 2.5 h, concentrated to 20 mL in vacuo, diluted with water, and extracted with ether. The ether was dried ($MgSO_4$) and evaporated to afford 1.395 g (77%) of *cis*-bromo *cis*-epoxide **25**. An analytical sample of **25** was obtained by evaporative distillation: NMR ($CDCl_3$) 1.38 and 2.01 (s and m, 18), 2.92 (m, 1, c-CHCO), 3.06 (m, 1, c-CHCO), and 3.63 ppm (m, 1, –CHBr); mass spectrum *m/e* 181 (38%) (P – Br).

Anal. Calcd for $C_{12}H_{21}BrO$: C, 55.18; H, 8.10. Found: C, 55.47; H, 8.38.

When a chloroform solution of *cis*-bromo *cis*-epoxide **25** was kept with 47% hydrobromic acid for 4 days there was obtained a 93% yield of an oil whose NMR spectrum was identical with that of *cis,trans*-2,12-dibromocyclododecanol (**22**).

***cis*-3-Bromo-*trans*-1,2-epoxycyclododecane (23).** A solution of 2.15 g (6.29 mmol) of *cis,cis*-2,12-dibromocyclododecanol (**20**) and 4.90 g (0.05 mol) of potassium acetate in 100 mL of acetone was kept at ambient temperature for 72 h. Workup afforded 1.12 g of an oil. The analytical sample of bromo epoxide **23** was obtained by evaporative distillation [40 °C (0.05 mm)]: NMR ($CDCl_3$) 1.4 and 2.10 (s and m, 18), 2.72 (t, 1, J = 2 Hz, c-CHCO), 3.10 (d of t, 1, J = 2, 10 Hz, c-CHCO), and 4.64 ppm (m, 1, –CHBr); mass spectrum *m/e* 181 (48%) (P – Br).

Anal. Calcd for $C_{12}H_{21}BrO$: C, 55.18; H, 8.10. Found: C, 55.00; H, 8.03.

When a chloroform solution of 0.375 g of *cis*-bromo *trans*-epoxide **23** was stirred with 20 mL of 47% hydrobromic acid for 24 h at ambient temperature there was obtained 0.297 g of oil whose NMR spectrum indicated the presence of 70% of *cis,cis*-2,12-dibromocyclododecanol (**20**) and 30% of an unidentified olefinic material.

***trans*-3-Bromo-*cis*-1,2-epoxycyclododecane (24).** To a solution of 0.726 g (2.12 mmol) of *trans,trans*-2,12-dibromocyclododecanol (**21**) in 50 mL of methanol was added 1.0 g (7.24 mmol) of potassium carbonate in 10 mL of methanol and 1 mL of water. The mixture was stirred overnight at ambient temperature and worked up to give an oil which solidified on standing. Recrystallization from pentane at −78 °C gave 0.371 g of pure bromo epoxide **24**: mp 47–49 °C; NMR ($CDCl_3$) 1.4 and 2.05 (s and m, 18), 3.07 and 3.21 (m, 2, c-CHCO), and 3.92 ppm (m, 1, –CHBr); mass spectrum *m/e* 181 (31%) (P – Br).

Anal. Calcd for $C_{12}H_{21}BrO$: C, 55.18; H, 8.10. Found: C, 55.09; H, 8.05.

A chloroform solution containing 0.5 g of *trans*-bromo *cis*-epoxide **24** was stirred with 15 mL of 47% hydrobromic to give 0.4 g (61%) of an oil whose NMR spectrum was identical with that of *trans,trans*-2,12-dibromocyclododecanol (**21**).

Lithium Aluminum Hydride Reduction of Dibromohydrins and Bromo Epoxides. A. *cis,cis*-2,12-Dibromocyclododecanol (20). A mixture of 0.384 g (1.12 mmol) of **20** and 0.0906 g (2.38 mmol) of lithium aluminum hydride in 15 mL of ether was refluxed for 20 h. Water was added slowly until the precipitate coagulated. The ether was decanted, dried ($MgSO_4$), and evaporated to leave an oil which was chromatographed on silica gel. Elution with 10% ether–pentane afforded unreacted **20** and 0.0862 g (39%) of solid whose melting point and NMR were identical with that of *cis*-2-bromocyclododecanol (**26**).

B. *trans,trans*-2,12-Dibromocyclododecanol (21). Heating a mixture of 0.85 g (2.48 mmol) of **21** with 0.19 g (5.02 mmol) of lithium aluminum hydride in 15 mL of ether as described above gave, after chromatography on silica gel using 10% ether–pentane as an eluant, dibromohydrin **21**, cyclododecanol, *trans*-bromo *cis*-epoxide **24**, and 0.047 g (7%) of *trans*-2-bromocyclododecanol (**29**).

C. *cis*-3-Bromo-*trans*-1,2-epoxycyclododecane (23). To a solution of 3.72 g (14.21 mmol) of epoxide **23** in 100 mL of ether was added 1.33 g (34.6 mmol) of lithium aluminum hydride and the mixture was stirred at ambient temperature for 24 h and then refluxed for 12 h. The mixture was poured into water, the layers were separated, and the aqueous phase was extracted with ether. The ether was dried ($MgSO_4$) and evaporated to leave 2.09 g of oil. Chromatography of 0.314 g of this oil on silica gel using 13% ether–pentane as eluant gave 0.033 g of epoxide **23**, 0.078 g (30%) of *cis*-2-bromocyclododecanol (**26**), and 0.137 g of a mixture of cyclododecanol and 2-cyclododecenol.

D. *trans*-3-Bromo-*cis*-1,2-epoxycyclododecane (24). A solution of 0.498 g (1.9 mmol) of *trans*-bromo *cis*-epoxide **24** in 18 mL of anhydrous THF was mixed with 9.33 mL of 0.3 M (2.8 mmol) lithium aluminum hydride in THF and the solution was kept at ambient temperature for 24 h. The solution was poured into water and extracted with ether. The ether was dried and evaporated to give 0.381 g (76%) of solid whose NMR was identical with that of *trans*-2-bromocyclododecanol (*29*).

E. *cis*-3-Bromo-*cis*-1,2-epoxycyclododecane (25). Treatment of 0.61 g (2.34 mmol) of epoxide **25** with 10.5 mL of 0.27 M (2.79 mmol) lithium aluminum hydride in THF as described above afforded a mixture whose NMR spectrum indicated the presence of epoxide **25**, 2-cyclododecenol, and *cis*-2-bromocyclododecanol (**26**) (~10%).

***cis*-2-Bromocyclododecanol (26).** Epoxidation of pure *trans*-cyclododecene[22] with *m*-chloroperbenzoic acid gave *trans*-cyclododecene oxide (**27**): NMR ($CDCl_3$) 1.1–2.4 (m, 20), 2.61 (m, 1, c-CHCO), and 2.76 ppm (m, 1, c-CHCO). Treatment of 2.63 g of *trans*-cyclododecene oxide (**27**) in chloroform with 3.0 mL of 47% hydrobromic acid afforded 3.27 g of *cis*-2-bromocyclododecanol (**26**): mp 62–63 °C (lit.[23] mp 64–65 °C); NMR ($CDCl_3$) 1.3–2.3 (m, 21, $-CH_2-$ and –OH), 3.88 (m, 1, –CHO–) and 4.35 ppm (m, 1, –CHBr).

cis-2-Bromocyclododecyl acetate (**26a**) was prepared in 90% yield by acetylation of **26** with acetyl chloride and magnesium powder and showed: IR 5.73 and 8.10 μm; NMR ($CDCl_3$) 1.35 and 2.0 (s and m, 20), 2.08 (s, 3, CH_3CO_2–), 4.26 (m, 1, –CHBr), and 5.18 ppm (m, 1, –CHOAc).

***trans*-2-Bromocyclododecanol (29).** Epoxidation of pure *cis*-cyclododecene[21] afforded *cis*-cyclododecene oxide (**30**): NMR 1.2–2.0 (m, 20), 2.78 (m, 1, c-CHCO) and 2.92 ppm (m, 1, c-CHCO). A solution of 1.60 g of epoxide **30** in chloroform was stirred overnight at ambient temperature with 1.5 mL of 47% hydrobromic acid to give 2.02 g of *trans*-2-bromocyclododecanol (**29**): mp 66–67 °C; NMR ($CDCl_3$) 1.3–2.1 (m, 20), 2.2 (s, 1, –OH), 3.78 (m, 1, c-CHCO), and 4.32 ppm (m, 1, –CHBr).

trans-2-Bromocyclododecyl acetate was obtained in 81% yield by acetylation of **29** with acetyl chloride in the presence of magnesium powder and showed: IR 5.72 and 8.1 μm; NMR 1.35 and 1.95 (s and m, 20), 2.06 (s, 3, CH_3CO_2–), 4.25 (m, 1, –CHBr), and 5.20 ppm (m, 1, –CHOAc).

Registry No.—**1,** 16080-75-4; **2,** 64714-59-6; **2a,** 64714-60-9; **3,** 56391-36-7; **3a,** 64714-61-0; **4,** 56421-06-8; **5,** 56421-05-7; **6,** 56391-35-6; **6** acetate, 64714-62-1; **7,** 16080-74-3; **10,** 7422-06-2; **11,** 64714-63-2; **12,** 64714-64-3; **12** acetate, 64714-65-4; **13,** 64714-66-5; **14,** 64714-67-6; **14** acetate, 64714-68-7; **15,** 64753-29-3; **16,** 64714-69-8; **16** acetate,

64714-70-1; **17**, 16110-80-8; **18**, 19914-84-2; **19**, 19914-85-3; **20**, 64753-30-6; **20a**, 64753-31-7; **21**, 64753-32-8; **21a**, 64753-33-9; **22**, 64714-55-2; **22a**, 64714-56-3; **23**, 64714-57-4; **24**, 64753-27-1; **25**, 64753-28-2; **26**, 61153-78-4; **26a**, 61177-56-8; **29**, 61247-14-1; **32** acetate, 61153-80-8; **30**, 1502-29-0; **31**, 64714-58-5; acetyl chloride, 75-36-5; 3-bromocyclohexene, 1521-51-3.

References and Notes

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Reaction of Lithium *N,N*-Dialkylamide Enolates with Trialkylchlorosilanes

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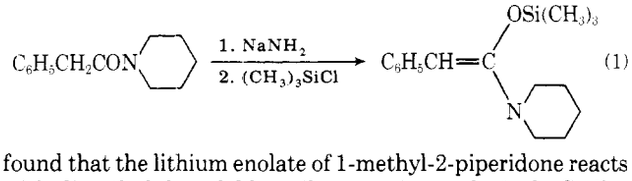
Lithium *N,N*-dialkylamide enolates were reacted in THF solution with trialkylchlorosilanes to give both C-silylated and O-silylated products. Acetamide enolates give predominantly C-silylation, while more highly substituted amide enolates give predominantly O-silylation with trimethylchlorosilane. *tert*-Butyldimethylchlorosilane gives increased amounts of O-silylation. Both C-silylated and O-silylated products hydrolyze with aqueous acid to the starting amide. O-Silylated compounds isomerize to C-silylated products on heating.

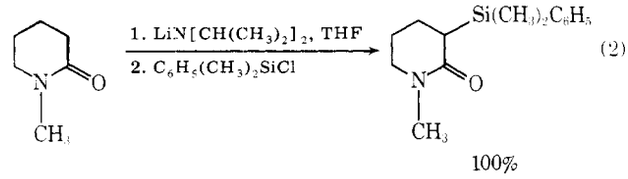
The reactions of ketone and ester enolates with trialkylhalosilanes have been studied extensively. Ketone enolates silylate exclusively at oxygen to form trialkylsilyl enol ethers.[1] Ester enolates, on the other hand, silylate at either oxygen (O-silylation) or at carbon (C-silylation) depending on the structure of the ester.[2]

In contrast, only fragmentary reports on the reaction of amide enolates with silylating reagents have appeared. Klebe reported that the sodium enolate of 1-phenylacetylpiperidide reacts with trimethylchlorosilane to give the O-silylated product, α-(1-piperidino)-β-phenyl-*O*-trimethylsilylvinyl ether, in unspecified yield (eq 1).[3] On the other hand, Trost

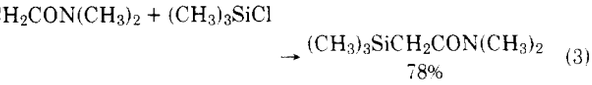


(1)

found that the lithium enolate of 1-methyl-2-piperidone reacts with dimethylphenylchlorosilane to give exclusively C-silylation (eq 2).[4] Most recently, Hudrlik reported that the lithium enolate of *N,N*-dimethylacetamide gave a 78% yield of the C-silylation product (eq 3), while the enolate of *N*-acetylaziridine gave a 33% yield of the O-silylation product (eq 4).[5]



(2)



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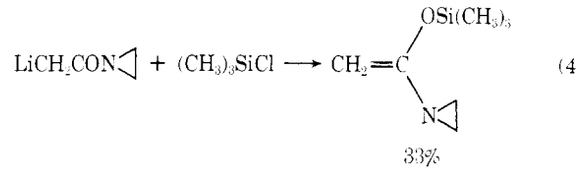

(4)

We recently reported that lithium *N,N*-dialkylamide enolates have appreciably greater stability than lithium ester enolates.[6] Considering the growing synthetic importance of the silyl derivatives of ester enolates,[7] we have undertaken a study of the reaction of *N,N*-dialkylamide enolates with trialkylhalosilanes. We report here the results of that study, together with information on the hydrolytic and thermal behavior of the products.

Results and Discussion

Silylation of Lithium Amide Enolates. Solutions of lithio *N,N*-dialkylamides were prepared by addition of the appropriate amide to tetrahydrofuran (THF) solutions of lithium diisopropylamide at 0 °C (eq 5).[6] The solutions were treated with a slight excess of silylating reagent (either trimethylchlorosilane or *tert*-butyldimethylchlorosilane) and then allowed to stir at room temperature for 30 min. The resultant

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