The Formation and Isomerization of 6,8-Dioxabicyclo[3.2.1]oct-2-ene and 6,8-Dioxabicyclo[3.2.1]oct-3-ene. A Note on the Course of α Halogenation of Acetals

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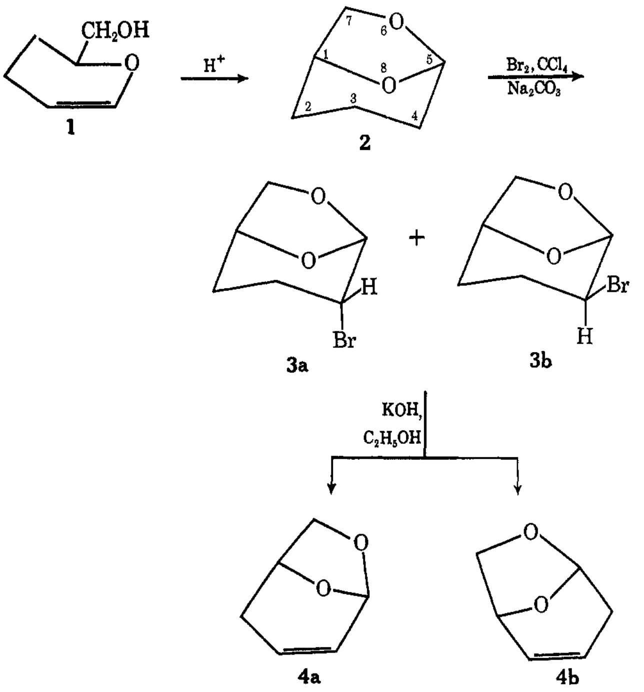
A previous report from this laboratory[2] has described the conversion of 2-hydroxymethyl-3,4-dihydro-2*H*-pyran (**1**) to 6,8-dioxabicyclo[3.2.1]oct-3-ene (**4a**) through the isolable intermediates **2** and **3** as shown in Scheme I. The product obtained from the bromination of 6,8-dioxabicyclo[3.2.1]octane (**2**) was thought to be the single compound *cis*-4-bromo-6,8-dioxabicyclo[3.2.1]octane (**3b**) because (1) gas–liquid chromatography (glc) of this product showed only one broad symmetrical peak, (2) the proton magnetic resonance (pmr) spectrum showed only one singlet ($W/2 = 3.5$ Hz) in the anomeric proton region, and (3) the low yield (30%) of the olefin **4a** obtained after a 24-hr treatment of **3** with hot ethanolic potassium hydroxide suggested that the bromine atom of the preferred chair conformation of **3** was not in a trans diaxial relationship with a vicinal hydrogen atom. There was no doubt that **4a** was the compound finally obtained[2] since it had been used to prepare 1,6-anhydro-4-deoxy-β-DL-xylohexopyranose[1] as well as DL-chalcose[3] both of which were adequately verified.

Scheme I



It has been observed in our work[4] that the base-catalyzed dehydrohalogenation of 3-bromo-2-ethoxytetrahydropyran (**5**), when carried out at temperatures above 100°, gave not only the expected 2-ethoxy-5,6-dihydro-2*H*-pyran (**6**), previously reported as the product obtained from the dehydrohalogenation of **5** with hot ethanolic potassium hydroxide,[5] but also 6-ethoxy-5,6-dihydro-2*H*-pyran (**7**). Pure **6** could also be converted partly to **7** by treatment with base, either for an extended period of time or at higher temperatures.[4] Preliminary work in this laboratory had also shown that pure **4a**, heated for 24–72 hr in refluxing ethanolic potassium hydroxide, gave a product which was found to be a mixture of the two olefins **4a** and **4b**.

In view of the potential value of the isomer **4b** in preparing 2-deoxy-DL-hexoses as well as 2,3-, 2,4-, or 3,4-dideoxy-DL-hexoses, we explored means of obtaining **4b** as the major if not the only product of dehydrohalogenation of **3**. The isomerization **4a** $\rightleftharpoons$ **4b** was also examined. In addition, the conversion **1** → **2** → **3** was reconsidered with a view to improvement of yields as well as to determine whether both possible isomers **3a** and **3b** were obtained from the bromination of **2**. This paper describes the results of the investigations.

Results and Discussion

Although variable yields of 40–65% have been reported[2] for the preparation of **2** from **1**, it is now found that the adoption of a minor but significant modification of the published precedure[2] provides **2** consistently in yields of 88–94%.

Even though the bromination of **2** has been reported to give **3** in yields of 60[3] and 73%,[2] these results could not be obtained consistently. The procedure in both reports[2,3] is based on that described for the bromination of acetals[6] and utilized finely divided anhydrous sodium carbonate suspended in a carbon tetrachloride solution of **2** to destroy the hydrogen bromide produced. When it became apparent that some hydrogen bromide was still present in the reaction mixture despite the presence of the suspended sodium carbonate, and that α halogenation of the acetals still proceeded well, the necessity for complete elimination of the halogen acid was questioned. Furthermore, the tendency of sodium carbonate to agglomerate prevented adequate dispersal of the reagents during the stirring of the reaction mixture. Accordingly, bromination was carried out in the absence of sodium carbonate, and this gave the monobromo product repeatedly in $\sim$80% yield. Under these conditions, the initial reaction was slow but soon became rapid when the concentration of the evolved hydrogen bromide increased. Most of the halogen acid was eliminated from the carbon tetrachloride solution because of its low solubility. This apparent "induction period" could be eliminated if dry hydrogen bromide was added to the carbon tetrachloride solution of **2** just before the addition of the bromine. Glc of the product on a *freshly prepared* column of 20% butanediol succinate on Chromosorb W showed *two* overlapping peaks in the area ratio of 3:2. It is significant that an old column showed only *one* broad symmetrical peak (*cf.* ref 2). Elemental analysis of this mixture agreed with that required for a monobromo-6,8-dioxabicyclo[3.2.1]octane; hence it was clear that bromination of **2**

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[2] F. Sweet and R. K. Brown, *Can. J. Chem.*, **46**, 2289 (1968).

[3] R. M. Srivastava and R. K. Brown, *ibid.*, **48**, 830 (1970).

[4] F. Sweet, U. Diner, H. Davis, and R. K. Brown, unpublished work.

[5] G. F. Woods and H. Sanders, *J. Amer. Chem. Soc.*, **68**, 2483 (1946).

[6] S. M. McElvain, R. L. Clarke, and G. D. Jones, *ibid.*, **64**, 1966 (1942).

gave a mixture of two isomeric monobromides, considered to be *trans*- and *cis*-4-bromo-6,8-dioxabicyclo[3.2.1]octane (**3a** and **3b**). These two products could not be separated by glc although ten different columns were tried.

When the mixture of isomers **3a** and **3b** was heated in refluxing ethanolic potassium hydroxide either for 24 hr as previously described[2] or for 1.5 hr, the same yield of olefinic material **4** was obtained, along with some unreacted 4-bromo-6,8-dioxabicyclo[3.2.1]octane. This recovered monobromo material, when analyzed by glc on two different columns, showed only one narrow symmetrical peak coincident in appearance time with the peak of the slower moving and minor component of the mixture **3a** and **3b**. When the recovered monobromo compound was subjected to an additional 24-hr treatment in refluxing ethanolic potassium hydroxide, little change occurred and it could be recovered in at least 83% yield. Only a trace of olefinic product could be detected by glc. The pmr spectrum of this recovered bromide showed a singlet at ($W/2 = 2.8$ Hz) at τ 4.6 in the anomeric proton region [*cf.* the singlet ($W/2 = 3.5$ Hz) at τ 4.6 for the mixture of **3a** and **3b** described previously[2]]. The 100-MHz pmr spectrum of this recovered monobromide permitted a decision that the disposition of the bromination is cis rather than trans to the five-membered ring of the bicyclo structure as indicated by structure **3b**. Signal assignments were readily made by double irradiation spin decoupling. Irradiation of the nuclei of the protons on C-3 giving the high field multiplet centered at τ 7.82 caused loss of a large coupling (~6–7 Hz) in the multiplet at τ 6.02, the position at which the absorption due to the proton on C-4 occurred. Irradiation at τ 6.02 gave a similar loss of coupling at τ 7.82. This large coupling can occur only if the two coupled protons on C-4 and C-3 are trans diaxial, and this requires that the six-membered ring be in the more stable chair conformation as expected. Structure **3b** but not **3a** has, in the chair conformation, the two protons on C-3 and C-4 in a trans diaxial relation. In this more stable conformation, the bromine atom on C-4 and the proton on C-3 of structure **3b** are not trans diaxially oriented, an orientation which is known to facilitate base-catalyzed removal of the halogen acid. On the other hand, in structure **3a** where the bromine atom is trans to the five-membered ring, the lower energy chair form does have the C-4 bromine trans diaxially disposed with respect to a proton on C-3. Hence the monobromo compound **3** which dehydrohalogenates more readily is considered to be **3a**, while that which is more resistant to removal of the halogen acid is believed to be **3b**.[7]

The olefinic material obtained by heating the mixture of **3a** and **3b** in refluxing ethanolic potassium hydroxide, when analyzed by glc on a freshly prepared column of butanediol succinate on Chromosorb W, showed two well-separated peaks in the area ratio of 1:9. These two components were readily separated by glc. A glc analysis of these separated compounds on two different columns gave only one symmetrical narrow peak in each case. The elemental analysis for each agreed with that required for the olefins **4a** and **4b**. A detailed first-order analysis of the 100-MHz pmr spectrum, using double irradiation to assist in identifying signals, agreed completely with the assignment of structure **4a** to the major isomer and **4b** to the minor isomer. A mixture of the two isolated olefins **4a** and **4b** gave a pmr spectrum identical with the spectrum reported[2] to be due to **4a**. The proportion of the two isomeric olefins **4a** and **4b** obtained depended upon the proportion of base to **3** used during dehydrohalogenation. If the molar ratio of base to **3** was 1:1 up to 3:1, only **4a** was obtained. The use of equimolar amounts of sodium hydride and **3** in 1,2-dimethoxyethane containing some ethanol has given **4a** exclusively.[8] Proportions of base to **3** greater than 3:1 gave increased amounts of **4b** relative to **4a**.

When either **4a** or **4b** was heated in a solution of potassium *tert*-butoxide in *tert*-butyl alcohol,[8] there was obtained a 50–65% yield of olefinic product which was found to be a mixture of **4a** and **4b** in the ratio of ~15:85, respectively. Since the isolated yield of olefin was only 50–65%, this proportion 15:85 can be considered at best as only *indicative* of an equilibrium mixture.

Dehydrohalogenation of the mixture of **3a** and **3b** with a hot (80°) solution of potassium *tert*-butoxide in *tert*-butyl alcohol gave in 40–45% yield a mixture of **4a** and **4b** generally in the proportion of 20–15:80–85. The major component **4b** could be separated quite readily by fractional distillation in a spinning-band column.

The exclusive attack of the bromine on the α position of the acetal[6] requires comment. Since (1) the presence of hydrobromic acid apparently increases the rate of bromination of **2**, and (2) it is known that distillation of 2-alkoxytetrahydropyrans in the presence of an acidic species such as phosphorus pentoxide or *p*-toluenesulfonic acid eliminates the alkoxy group and provides a 3,4-dihydro-2*H*-pyran,[9-11] and (3) it is also known that bromination of α,β-unsaturated ethers in alcohol solution containing ammonia[12] or silver carbonate[13] produces α-bromoacetals, the routes A and/or B shown in Scheme II are suggested as reasonable paths by which acetals or ketals are halogenated exclusively in the α position. The key step following the protonation of the acetal **2** is the cleavage of the C-5,O-6 or C-5,O-8 bond to form the oxocarbonium ion **8** and/or **9** which respectively would readily lose a proton to form the α,β-unsaturated ether **10** and/or **1**. The attack by bromine on **10** or **1** would form the β-bromooxocarbonium ion **11** and **12** or the α,β-dibromide **13** and **14**. By an intramolecular reaction involving the hydroxy group, any of the last four species could form the α-bromo acetal **3**. In support of Scheme II we have treated **1** with bromine under the same conditions used to brominate **2** and obtained a 65% yield of an approximately 1:1 mixture of **3a** and **3b**. The relative effectiveness of path a compared to path b is not known. For the moment we prefer route b on the basis of an apparently greater ease of C-5,O-6 bond cleavage in the hydrolysis or alcoholysis

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[7] It has been suggested by the referee that the transition state for the dehydrohalogenation might be syn, and if this were the case for both **3a** and **3b** one could account for the greater resistance of **3b** to dehydrohalogenation since this would require the more difficult approach by base to the endo face of **3b** compared to the easier approach of base to the exo face of **3a**.

[8] D. L. Griffith, D. L. Meges, and H. C. Brown, *Chem. Commun.*, 90 (1968).

[9] W. E. Parham and H. E. Holmquist, *J. Amer. Chem. Soc.*, **73**, 913 (1951).

[10] M. Julia and B. Jacquet, *Bull. Soc., Chim. Fr.*, 1983 (1963).

[11] R. M. Srivastava and R. K. Brown, *Can. J. Chem.*, **48**, 2341 (1970).

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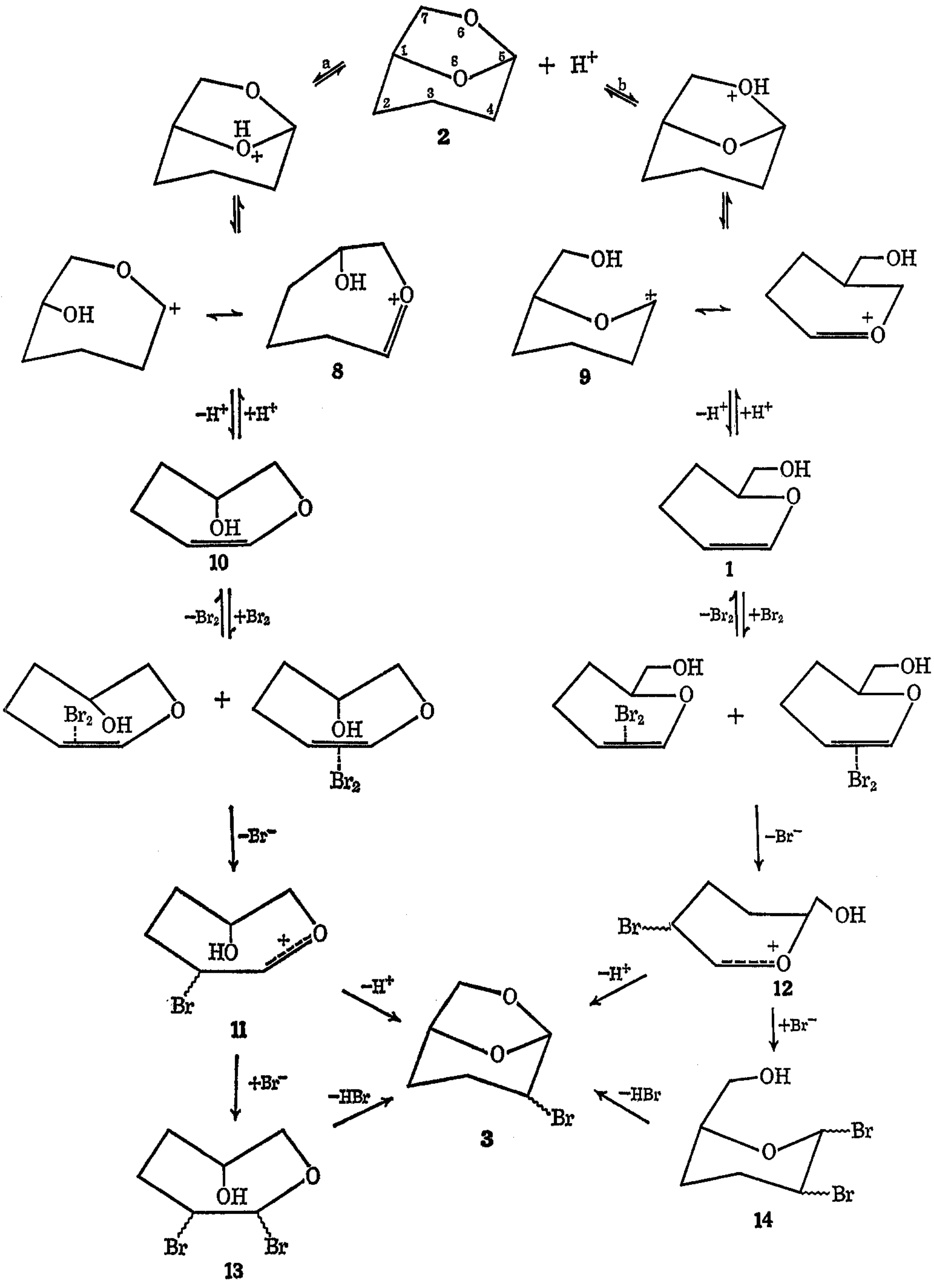
[13] R. U. Lemieux and B. Fraser-Reid, *ibid.*, **43**, 1460 (1965).

SCHEME II



of substituted bicyclic structures such as 2 to produce only the substituted pyran structure. However the substituted pyran so obtained may have been the result of accumulation of the thermodynamically more stable product and thus may not support the view that the C-5,O-6 bond cleaves much more readily than does the C-5,O-8 bond.

Experimental Section

All boiling points are uncorrected. Glc analyses were made with an F & M Model 700 chromatograph equipped with a column ($^1/_8$ in. × 12 ft) containing either 20% butanediol succinate on Chromosorb W (60–80 mesh) or 10% Reoplex (polypropylene adipate) on 80–100 mesh Chromosorb WAW (DMCS 5750). Helium was the carrier gas. Pmr spectra were taken in $CDCl_3$ and referred to tetramethylsilane.

6,8-Dioxabicyclo[3.2.1]octane (2).—Compound 2 was prepared according to published directions[2] but with the following modification. The amount of sodium methoxide added to the cooled solution of 1 and *p*-toluenesulfonic acid catalyst was doubled to ensure complete neutralization of the acid, thus preventing polymerization with consequent loss of product. The yield of 2 was 88–94%.

4-Bromo-6,8-dioxabicyclo[3.2.1]octane (3). **A. From 2.**—To a well-stirred solution of 2 (83.3 g, 0.73 mol) in 1.5 l. of dry CCl_4 was added dropwise a solution of bromine (116 g, 0.73 mol) in an equal volume of dry CCl_4. Bromine consumption occurred slowly at first but soon increased in rate as the concentration of evolved hydrogen bromide increased. The rate of bromine addition was adjusted so that the reaction was under control, requiring 1 hr total time for complete addition. When the last of the bromine had been added, the solvent was removed on a rotatory evaporator under vacuum at a *maximum* bath temperature of 30°. The residual light brown oil was distilled under vacuum in an apparatus equipped with a potassium hydroxide trap and afforded 112 g (80%) of 3, bp 60° (0.2 mm) [lit.[2] bp 68° (1 mm)]. Glc analysis on a freshly prepared column containing the butanediol succinate, and on a column packed with the Reoplex, showed in both cases two overlapping peaks in the area ratio of 3:2 corresponding to **3a** and **3b**, respectively.

B. From 1.—To a stirred solution of 22.8 g (0.20 mol) of **1** in 300 ml of dry carbon tetrachloride at room temperature was added dropwise over a period of 1 hr 32 g (0.20 mol) of bromine dissolved in 50 ml of dry carbon tetrachloride. The reaction mixture became warm (~45°) and evolved hydrogen bromide profusely. When the bromine addition was completed, the mixture was freed from solvent in a rotary evaporator under vacuum during which time the temperature of the mixture was kept below 30°. The light brown oily residue was distilled in an apparatus equipped with two potassium hydroxide traps and gave 14.9 g (65%) of 4-bromo-6,8-dioxabicyclo[3.2.1]octane (**3**) boiling at 64° (0.5 mm). Glc on either or the two columns showed it to be identical in retention time with **3** obtained from **2** above and that it was an approximately 1:1 mixture of **3a** and **3b**.

Dehydrohalogenation of 4-Bromo-6,8-dioxabicyclo[3.2.1]octane (3). A. With a 1 or 2 *M* Excess of Potassium Hydroxide in 95% Ethyl Alcohol.—The published directions[2] were modified as follows. To a stirred solution of 56 g (1.0 mol) of potassium hydroxide in 900 ml of 95% ethyl alcohol was added 96.5 g (0.50 mol) of the cis–trans mixture **3ab**. The resulting solution was heated under reflux for 24 hr and then cooled and filtered. The solvent (700 ml) was removed by fractional distillation at atmospheric pressure. Water (200 ml) was added to the residual dark mass and the mixture was then continuously extracted with ether for 10 hr. The ether extract was dried ($MgSO_4$) and freed from solvent by fractional distillation. The remaining black oil was distilled under reduced pressure and gave 21.8 g (39%) of 6,8-dioxabicyclo[3.2.1]oct-3-ene (**4a**): bp 58° (15 mm); $n^{25}D$ 1.4775 [lit.[3] bp 83–84° (51.5 mm); $n^{22}D$ 1.4795]; 100-MHz pmr τ 4.18 (m, 2, vinyl), 4.52 (m, $W/2 \sim 5$ Hz, 1, anomeric H), 5.35 (m, 1, HCO), 6.06 (t, 1, HCO), 6.33 (d, 1, HCO), 7.22 (d, 1, CH aliphatic), and 8.13 (d, 1, CH aliphatic). Glc on both columns showed only one narrow symmetrical peak.

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.04; H, 7.23.

The recovered bromide **3b** boiled at 71° (1.0 mm): $n^{27}D$ 1.5156 [lit.[2] of mixture **3a–b**, bp 68° (1 mm) or 90° (4.5 mm); $n^{27}D$ 1.5176]; glc analysis on either of the columns used showed only one narrow symmetrical peak; 100-MHz pmr τ 4.61 (s, 1, anomeric), 5.41 (m, 1, HCO), 6.05 (m, 3, CH_2O and HCBr), and 8.10 (m, 4, CH_2). Irradiation at τ 6.02 gave loss of coupling of ~6-7 Hz in the multiplet at τ 7.82 due to the two protons on C-3.

B. With Potassium *tert*-Butoxide in *tert*-Butyl Alcohol.—To a stirred solution of 0.75 mol of potassium *tert*-butoxide from 28.6 g of potassium metal slowly added to 750 ml of dry *tert*-butyl alcohol under N_2 was added 48.2 g (0.25 mol) of *cis,trans*-4-bromo-6,8-dioxabicyclo[3.2.1]octane (**3**). The mixture was kept at 80° for 24 hr and then half of the solvent was removed by fractional distillation. The dark residue was cooled and diluted with 250 ml of water. The resulting mixture was continuously extracted with ether for 12 hr. The ether extract was dried ($MgSO_4$) and freed from solvent by fractional distillation, and the residue distilled under vacuum to give 10 g (36%) of a 4:96 mixture (by glc) of the olefins **4a** and **4b**, respectively, bp 58–60° (16 mm), along with 12.3 g of **3b**, bp 72° (1.5 mm). The mixture of **4a** and **4b** was separated by distillation with a spinning-band column (50 cm): bp of **4b** 69–69.5° (41 mm); $n^{25}D$ 1.4750; 100-MHz pmr τ 4.14 (m, 2, vinyl), 4.34 (broad s, 1, anomeric H), 5.4 (t, 1, HCO), 6.02 (d, 1, HCO), 6.28 (t, 1, HCO), 7.47 (d, 1, CH aliphatic), and 8.03 (d, 1, CH aliphatic). Glc on both columns showed only one narrow symmetrical peak.

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.24; 63.99; H, 7.31; 7.22.

One of the repetitions of this experiment gave a yield of 44% of a 21:79 ratio of **4a**:**4b** as the lowest proportion of **4b** obtained.

Isomerization of 4a and 4b. A. With Potassium *tert*-Butoxide in *tert*-Butyl Alcohol.—A solution of potassium *tert*-butoxide in *tert*-butyl alcohol [from 3.13 g (0.08 g-atom) of potassium added to 80 ml of dry *tert*-butyl alcohol] containing 4.88 g (0.04 mol) of **4a** was kept under N_2 at 80° for 24 hr. Subsequent treatment followed that described in B above. There was obtained 2.40 g (49%) of a 20:80 mixture of the olefins **4a** and **4b**, respectively (by glc), bp 59° (15 mm).

When 5.60 g (0.05 mol) of **4b** was treated similarly with 0.051 mol of potassium *tert*-butoxide in *tert*-butyl alcohol, there was obtained 3.50 g (63%) of a 15:85 mixture of the olefins **4a** and **4b**, respectively (by glc).

B. With Potassium Hydroxide in 95% Ethyl Alcohol.—A solution of 21 g (0.188 mol) of a 19:1 mixture of **4a** and **4b** and 36.8 g (0.65 mol) of potassium hydroxide in 180 ml of 95% ethyl alcohol was heated under reflux (N_2) for 24 hr. The solvent was then removed by fractional distillation. The residue, diluted with water, was extracted several times with ether. The combined ether extracts were dried (Na_2SO_4) and freed from solvent. Fractional distillation of the residue under vacuum gave 12.6 g (60%) of a colorless liquid, bp 58–62° (9 mm), $n^{23}D$ 1.4775. Glc analysis produced two well-separated narrow peaks which showed this to be a mixture of **4a** and **4b** in the ratio 2:3, respectively.

Registry No.—**4a**, 20583-51-1; **4b**, 27925-22-0.

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Conformational Analysis of Sulfur-Containing Heterocycles. A Dipolar Effect[1]

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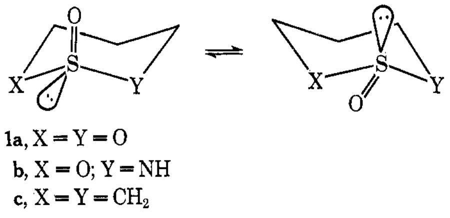
The conformational preferences for substituents on cyclohexane ring systems are well studied.[3] However, when heteroatoms containing nonbonded lone-pair electrons are present, conformational effects may be altered considerably.[4] The conformational preference for an axial disposition of a sulfoxide oxygen is very small (0.1–0.5 kcal).[5] It is therefore surprising that sulfoxides of the type **1** where X and Y are heteroatoms exhibit a remarkably high axial preference (3–5 kcal/mol).[6] The substitution of a heteroatom for a methylene group in such systems should lower the barrier to chair–chair interconversion by reducing 1–2 rotational interactions.[7] Moreover, Eliel[4a] has demonstrated that sulfur (presumably oxygen as well) with its lone pairs has a smaller space requirement than a methylene group. While there have been several explanations advanced[5] for the small preference for axial S=O in **1c**, the question remains open as to why



1a, X = Y = O
b, X = O; Y = NH
c, X = Y = CH_2

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[2] Holder of a NRCC Scholarship, 1968–1970.

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