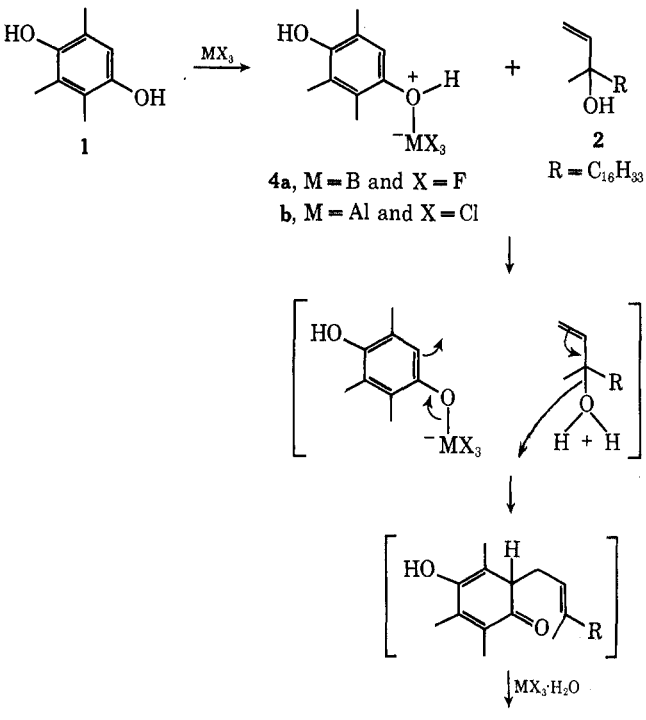
SCHEME II



pure trimethylhydroquinone (recrystallized from monochlorobenzene, mp 172–174°, slightly ground material containing no lumps) and the mixture was swirled until all material was dissolved (under N_2, color change to green). After about 2 min, rapid crystallization of the complex was observed. The reaction mixture was allowed to stand without stirring for 3 hr at room temperature before the crystals were filtered under N_2. After two washings with CH_2Cl_2 (10 ml and 15 ml, always under N_2) the material was dried directly with a high vacuum pump. The resulting 12.5 g (87.7%) of grayish looking crystals were used for analysis: ir (Nujol)[8] 3500 m, 1630 w ($AlCl_3$ absorption), 1310 m, 1180 s, 1080 s, 830 m, 720 m, 535 s cm^{-1}.

Anal. Calcd for $C_9H_{12}O_2 \cdot AlCl_3$: C, 37.86; H, 4.24; Cl, 37.25. Found: C, 38.46; H, 4.42; Cl, 35.31.

***dl*-α-Tocopherol *via* TMHQ–BF_3 Complex.**—Trimethylhydroquinone (46.0 g, 0.303 mol), 250 ml of CH_2Cl_2, and 18 ml (20.4 g, 0.334 mol) of CH_3NO_2 were put into a 500-ml three-necked flask and blanketed with N_2. The flask was then immersed in a cooling bath at −20°. With continuous stirring, a strong flow of BF_3 gas (the cyclinder was mounted on a scale) was passed into the suspension of trimethylhydroquinone. At the beginning of the BF_3 addition the color turned green, the suspension became thinner, and after approximately 5 min crystallization of the boron trifluoride–trimethylhydroquinone complex started. The appearance of the reaction mixture changed to a beige color and the contents were a readily stirrable slurry. After *ca.* 20 min a total of 20.6 g (0.304 mol) of BF_3 had been introduced (the rate of the BF_3 flow was controlled by a gas washing bottle containing CH_2Cl_2). During this time, the temperature fell from initially 20° to −20°. At this point, slow subsurface addition of 100 g (0.338 mol) of isophytol was started by way of a peristaltic pump. The temperature was maintained at −20°. The color of the reaction mixture changed from beige *via* yellow to an amost clear dark brown at the end of the 2–3 hr addition period. The stirring was maintained for an additional 1 hr before the reaction mixture was transferred to a separatory funnel using a small amount of CH_2Cl_2 for rinsing the three-necked flask. This solution was washed under N_2 three times with a total of 400 ml of distilled H_2O (200, 100, 100 ml; *no heat generation* was observed with the first H_2O addition). The water layers in turn were washed with 50 ml of CH_2Cl_2. After combination of all yellow-orange layers and evaporation of the solvent at the rotavap, the residue was dissolved in 200 ml of hexane and washed with five 50-ml portions of 78% CH_3OH–H_2O mixture. Each H_2O phase was reextracted with 50-ml portions of hexane. After combination of all organic layers and evaporation of the hexane at the rotavap, there was obtained 143–146 g of orange-colored crude *dl*-tocopherol. This residue, on simple high-vacuum distillation through a 5-cm Vigreux adapter, yielded a light yellow-colored main fraction, 120 g (82% based on isophytol), bp 220–239° (0.07–0.1 mm).[9] This material assayed >98% by vpc.

***dl*-α-Tocopherol *via* TMHQ–$AlCl_3$ Complex.**—Into a stoppered three-necked flask (rinsed with dry N_2), 33.7 g (0.252 mol) of $AlCl_3$ powder (Baker, AR grade) was weighed, the flask was immersed in a cooling bath at 0°, and 250 ml of CH_2Cl_2 was added. To the stirred suspension, cooled to 0° while a slow flow of N_2 was maintained throughout the procedure, 33.7 ml (38.2 g, 0.626 mol) of CH_3NO_2 was added. All the $AlCl_3$ dissolved and the temperature rose to 12°. After the temperature had dropped to 0° again, the stirring was stopped[10] and 51.4 g (0.338 mol) of trimethylhydroquinone was added through a powder funnel. The stirrer was started again and the solid material almost dissolved with a color change to dark green (no rise in temperature was observed.). With continued stirring the contents were cooled to −20°. After *ca.* 3–5 min a very fine reaction intermediate started to crystallize and it was necessary to increase the rate of stirring. The heat of crystallization increased the temperature by about 2 or 3°. The color was now light yellow and the slurry was readily stirrable. As soon as the temperature reached −20°, 100 g (0.388 mol) of isophytol was introduced in the same manner as in the experiment described for the TMHQ–BF_3 complex. Analogous work-up and high vacuum distillation of the crude *dl*-α-tocopherol yielded a main fraction of 111.4 g (76.4%), bp 215–232° (0.07 mm). Vpc analysis indicated the vitamin E thus obtained to have a purity in excess of 98%.

Registry No.—**3**, 364-50-1; **4a**, 30783-58-5; **4b**, 26162-55-0.

Acknowledgment.—We are indebted to the staff of our Physical Chemistry Department directed by Dr. P. Bommer. In particular we thank Dr. F. Scheidl for the microanalyses, Mr. J. Manius for gas chromatographic analyses, and Mr. S. Traiman for ir spectra.

(8) Cell preparation was carried out in a drybox.

(9) Bp 200–220° (0.1 mm): The Merck Index, 8th ed, 1968, p 114.

(10) This must be done to prevent crystallization of the trimethylhydroquinone–aluminum chloride complex before all the trimethylhydroquinone has been added.

A Study of Syn/Anti Oxime Ratios from the Paramagnetic-Induced Shifts in the Proton Magnetic Resonance Spectra Using Tris(dipivalomethanato)europium(III)[1a]

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Tris(dipivalomethanato)europium(III) [Eu(DPM)$_3$] has been recently used to effect paramagnetic-induced shifts in the proton magnetic resonance spectra of alcohols and amines.[2-4] We have found that this reagent has considerable value in the study of syn–anti isomerism in oximes. Nuclear magnetic resonance

(1) (a) Supported by Public Health Service, Cancer Institute, Grant CA-07202-09; (b) Research Associate, 1969–1972.

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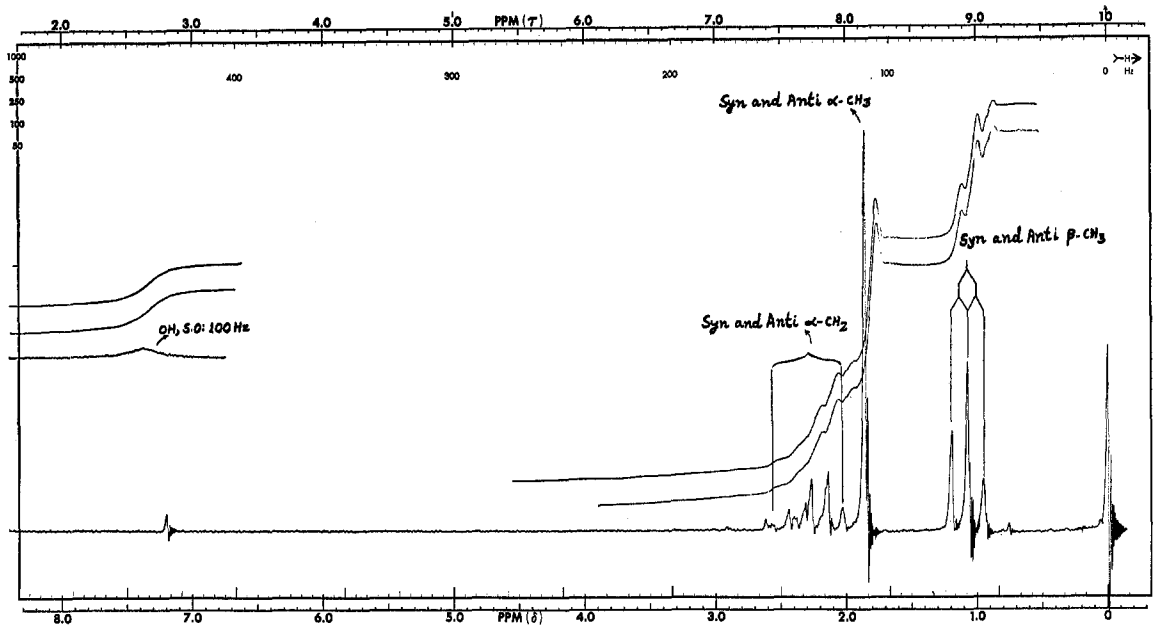

Figure 1.—Nmr spectrum of **1** in $DCCl_3$ (0.001 mol in 0.5 ml).

TABLE I

α-METHYL RESONANCES[a] FOR OXIMES **1–6** IN $DCCl_3$[b] (δ) AND IN $DCCl_3$–Eu(DPM)$_3$[c] (δ*)

R_1R_2C=NOH								
R_1	R_2	Oxime	δ (syn)	δ* (syn)	Δδ (syn)	δ (anti)	δ* (anti)	Δδ (anti)
CH_3	CH_2CH_3	**1**	1.86	2.12	0.26	1.83	2.72	0.89
CH_3	$(CH_2)_2CH_3$	**2**	1.85	2.17	0.32	1.81	3.01	1.20
CH_3	$(CH_2)_4CH_3$	**3**	1.83	2.13	0.30	1.81	2.85	1.04
CH_3	$(CH_2)_5CH_3$	**4**	1.83	2.15	0.32	1.81	2.91	1.10
CH_3	$CH(CH_3)_2$	**5**	1.82	2.05	0.23	1.76	3.11	1.35
CH_3	$CH_2CH(CH_3)_2$	**6**	1.83	2.03	0.20	1.83	2.97	1.14

[a] Chemical shifts in δ; TMS internal reference. [b] 0.001 mol of the oxime in 0.5 ml of $DCCl_3$. [c] 0.001 mol of the oxime in 0.5 ml of $DCCl_3$ containing 20 mg (2.8×10^{-5} mol) of Eu(DPM)$_3$.

TABLE II

α-METHYLENE OR α-METHINE RESONANCES[a] FOR OXIMES **1–6** IN $DCCl_3$[b] (δ) AND IN $DCCl_3$–Eu(DPM)$_3$[c] (δ*)

R_1R_2C=NOH								
R_1	R_2	Oxime	δ (syn)	δ* (syn)	Δδ (syn)	δ (anti)	δ* (anti)	Δδ (anti)
CH_3	CH_2CH_3	**1**	2.21 (q)[d]	2.58 (q)	0.37 (q)	2.38 (q)	3.05 (q)	0.67 (q)
CH_3	$(CH_2)_2CH_3$	**2**	2.17 (t)[d]	2.60 (t)	0.43 (t)	~2.33 (t)	3.25 (t)	0.92 (t)
CH_3	$(CH_2)_4CH_3$	**3**	~2.15 (t)[d]	2.55 (t)	0.40 (t)	~2.21 (t)	3.13 (t)	0.92 (t)
CH_3	$(CH_2)_5CH_3$	**4**	~2.17 (t)[d]	2.57 (t)	0.40 (t)	~2.22 (t)	3.20 (t)	0.98 (t)
CH_3	$CH(CH_3)_2$	**5**	~2.37 (m)[e]	2.77 (m)	0.40 (m)	~2.37 (m)	4.70 (m)	2.40 (m)
CH_3	$CH_2CH(CH_3)_2$	**6**	~2.07 (d)[e]	2.31 (d)	0.24 (d)	~2.07 (d)	3.15 (d)	1.08 (d)

[a] Chemical shifts in δ; TMS internal reference. [b] 0.001 mol of the oxime in 0.5 ml of $DCCl_3$. [c] 0.001 mol of the oxime in 0.5 ml of $DCCl_3$ containing 20 mg of Eu(DPM)$_3$. [d] α-Methylene resonances. [e] α-Methine resonances: d = doublet; t = triplet; q = quartet; m = multiplet.

spectroscopy has been applied earlier to the study of syn–anti isomerism in oximes[5-13] but extensive overlap of signals prevented unequivocal analysis. Lustig[5] observed syn–anti isomerism in several aliphatic ketoximes as indicated by the presence of two resonance lines for the protons on carbon atoms next to the oximino group. He found that the frequency of resonance lines of these protons differs only when certain aromatic solvents are used, and the separation of lines depends on concentration. Karabatsos and coworkers[13] have also detected similar solvent-induced shifts in the syn and anti isomers of oximes. They observed that the $\Delta\nu$ value ($\Delta\nu$ = ν in aromatic solvent − ν in carbon tetrachloride both with respect to TMS) for protons trans to the oxime hydroxyl group is greater than the $\Delta\nu$ value for the same proton when cis to the hydroxyl. Recently, benzene solutions of oximes containing hydrogen chloride gas have been shown to give somewhat improved separation of resonance lines for syn and anti isomers.[14] Since hydrogen chloride is known to catalyze syn–anti isomerism in oximes,[15] this method has to be used with caution.

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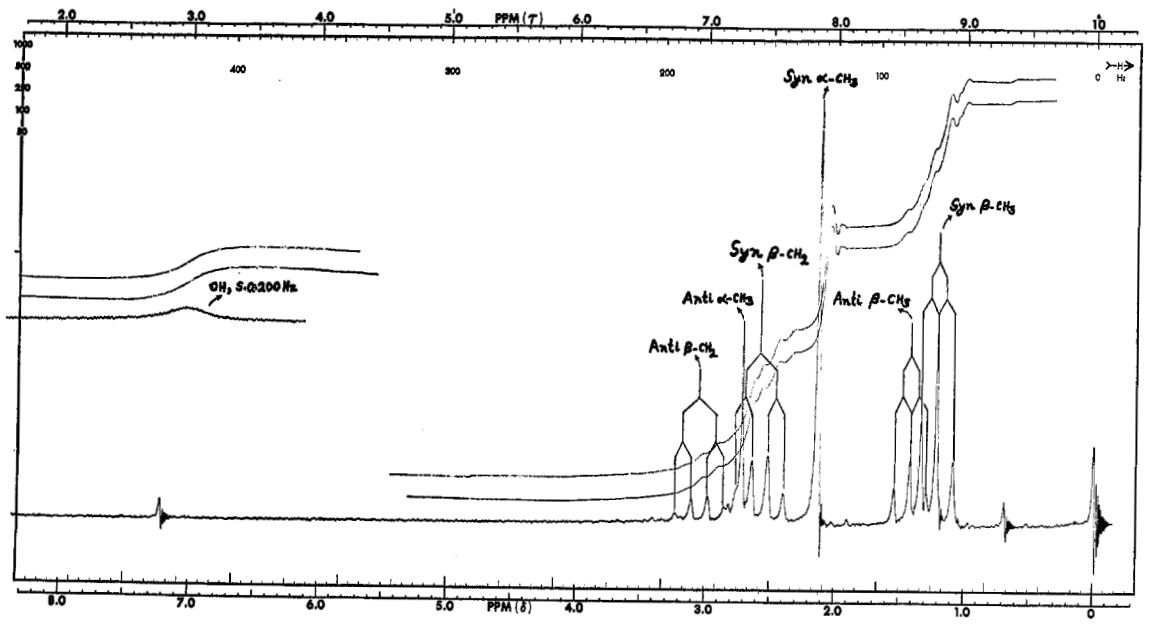

Figure 2.—Nmr spectrum of **1** in $DCCl_3$ (0.001 mol in 0.5 ml of $DCCl_3$) containing 20 mg of $Eu(DPM)_3$.

TABLE III

SYN-ANTI PERCENTAGES[a]

$R_1R_2C{=}NOH$				
R_1	R_2	Oxime	% syn	% anti
CH_3	CH_2CH_3	1	72	28
CH_3	$(CH_2)_2CH_3$	2	73	27
CH_3	$(CH_2)_4CH_3$	3	75	25
CH_3	$(CH_2)_5CH_3$	4	74	26
CH_3	$CH(CH_3)_2$	5	86	14
CH_3	$CH_2CH(CH_3)_2$	6	71	29

[a] From the nmr spectra of 0.001 mol of the oxime in 0.5 ml of $DCCl_3$ containing 20 mg of $Eu(DPM)_3$.

In the present study we have observed dramatic separation of resonance lines for the syn and anti isomers for a number of alkyl methyl ketoximes **1–6** (Table I and II, Figures 1 and 2) in the presence of Eu-

$(DPM)_3$. The separation of resonance lines was sufficiently large that an accurate ratio of the two forms could be obtained directly from the nmr spectra (Table III). That the syn forms are present in larger amounts in this series of oximes **1–6** was confirmed by the Beckmann rearrangement of methyl isopropyl ketoxime (**6**) using PCl_5. A mixture of *N*-isopropylacetamide and *N*-methylisobutyramide was obtained in the ratio of 86:14.

For the paramagnetic-induced shifts produced by $Eu(DPM)_3$ with alcohols, coordination of the metal complex with the hydroxyl lone pair of electrons has been proposed.[2-4] In the case of oximes there are two sites available for coordination, namely the oxygen lone pair and the nitrogen lone pair. With the present results it is difficult to assign with certainty the coordination site. However, one interesting observation is that all protons of the anti forms are more deshielded than the corresponding protons of the syn form. This suggests that the coordination occurs through the nitrogen lone pair. One explanation for the increased deshielding in the anti forms is on the basis of better coordination between $Eu(DPM)_3$ and the nitrogen lone pair due to less hindrance between $Eu(DPM)_3$ and the methyl group. In the syn form, coordination on the nitrogen lone pair may be less effective compared to that in the anti form because of the steric effect of the larger alkyl group. Regarding coordination with $Eu(DPM)_3$, Sanders and Williams[4] have shown that many amines coordinate better than alcohols.

TABLE IV

δ (SYN) − δ (ANTI) ($\Delta\delta$) IN PARTS PER MILLION FOR THE OXIMES[a]

$R_1R_2C{=}NOH$		$\Delta\delta$ (α-CH_3)		$\Delta\delta$ (α-CH_2)		$\Delta\delta$ (β-CH_3)	
R_1	R_2	$DCCl_3$ + $Eu(DPM)_3$[b]	C_6D_6	$DCCl_3$ + $Eu(DPM)_3$	C_6D_6	$DCCl_3$ + $Eu(DPM)_3$	C_6D_6
CH_3	CH_2CH_3	+0.6	−0.1	−0.49	−0.32	−0.22	0.00
CH_3	$CH(CH_3)_2$	+1.08	−0.16			−0.43	+0.06

[a] Negative values mean that the proton cis to the hydroxy group resonates at a lower field than trans; positive values mean the reverse. [b] Data from solutions of 0.001 mol of oxime in 0.5 ml of $DCCl_3$ containing 20 mg of $Eu(DPM)_3$. [c] Data from ref 12.

The shifts caused by $Eu(DPM)_3$ are even greater than those induced by the use of C_6D_6 or benzene. A comparison of $\Delta\delta$ [δ (anti) − (δ) syn in parts per million] values obtained by Karabatsos and coworkers[13] with the present method for two oximes **1** and **5** (Table IV) shows that the $\Delta\delta$ values for the α-methyl group obtained in the present study are at least six times larger than the $\Delta\delta$ values from C_6D_6 solutions of the oxime. $\Delta\delta$ values for other protons are also larger in $DCCl_3$ containing $Eu(DPM)_3$ than in C_6D_6.

Experimental Section

Preparation of Oximes.—Oximes were prepared by reacting the ketones (0.1 mol) with hydroxylamine hydrochloride (0.15

mol) in boiling ethyl alcohol (100 ml) containing pyridine (5 ml) as base and then purified by distillation. All of the oximes are known.

Nmr Spectra.—Nmr spectra were determined at 60 MHz on a Varian A-60 spectrometer in $DCCl_3$ solutions (0.001 mol of oxime in 0.5 ml of $DCCl_3$) with TMS as internal reference. Tris(dipivalomethanato)europium(III) (Alfa Inorganics, Beverly, Mass.) (20 mg) was added to the above $DCCl_3$ solutions and spectra were recorded again.

Beckmann Rearrangement of Methyl Isopropyl Ketoxime.—To the oxime **6** (1.01 g, 0.01 mol) in 25 ml of dry ether, PCl_5 (3.12 g, 0.015 mol) was added in small quantities with stirring. After the addition, the mixture was stirred at room temperature for 30 min and poured into excess water. The water solution was extracted with chloroform. The chloroform extract was washed (H_2O) and dried ($MgSO_4$). Evaporation of chloroform gave 1 g (quantitative) of the mixture of *N*-isopropylacetamide and *N*-methylisobutyramide in the ratio of 86:14 [estimated from nmr (CCl_4) δ 1.87 (s, $COCH_3$ protons of *N*-isopropylacetamide[16]) and δ 2.70 (d, J = 5 Hz, *N*-methyl protons of *N*-methylisobutyramide)[17]]. Nmr data for both amides are recorded.[16,17]

Registry No.—**1** (*E*), 10341-63-6; **1** (*Z*), 10341-59-0; **2** (*E*), 26306-10-5; **2** (*Z*), 26306-11-6; **3** (*E*), 30669-60-4; **3** (*Z*), 30669-61-5; **4** (*E*), 10341-61-4; **4** (*Z*), 10341-58-9; **5** (*E*), 10341-62-5; **5** (*Z*), 10341-60-3; **6** (*E*), 30669-66-0; **6** (*Z*), 30669-67-1; tris(dipivalomethanato)eurapium(III), 15522-71-1.

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Bromohydrins of Methylenecyclobutane

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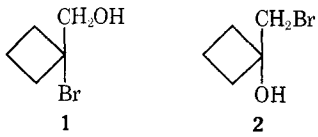
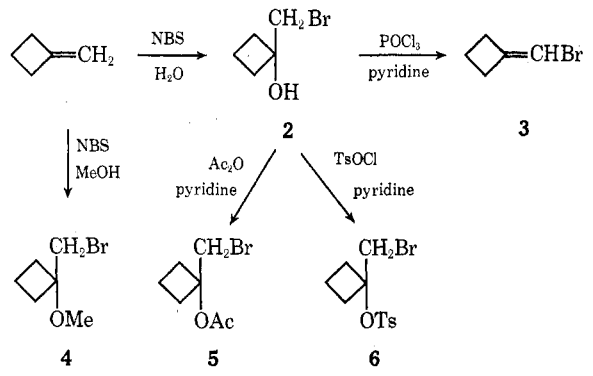
In connection with another investigation[1] we had need of 1-bromo-1-(hydroxymethyl)cyclobutane (**1**). This material had been reported[2] as essentially the only product formed in the treatment of methylenecyclobutane with hypobromous acid. We have repeated this work and have found that the major product is not **1** but its isomer, 1-(bromomethyl)cyclobutanol (**2**). An analogous misassignment of structure[2] in the case of the six-membered ring series has previously been noted.[3]



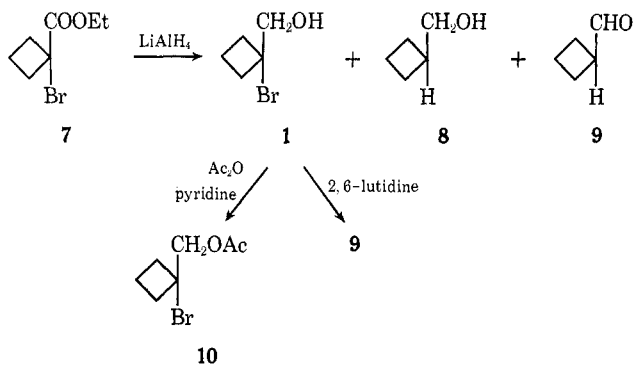
1 **2**

The reaction of methylenecyclobutane with aqueous *N*-bromosuccinimide (NBS) proceeds rapidly at ice temperature. Distillation of the resultant product affords **2** in about 90% purity. A minor product, possibly **1**, is also formed but is quite unstable, eliminating hydrogen bromide to produce a carbonyl compound.

1-(Bromomethyl)cyclobutanol (**2**) forms an acetate and a tosylate, neither of which eliminated hydrogen bromide readily when treated with base. Dehydration of **2** occurred, however, to give bromomethylenecyclobutane (**3**). This latter transformation establishes the position of the bromine atom in **2**. Analogously, the reaction of methylenecyclobutane with NBS in anhydrous methanol afforded one major bromo ether, assigned structure **4**. This assignment is based upon the method of preparation of **4** (same conditions as for **2**) and a comparison of its nmr spectrum with that of **2** (see Experimental Section).



1-Bromo-1-(hydroxymethyl)cyclobutane (**1**)[4] was prepared by reduction of ethyl 1-bromocyclobutylcarboxylate (**7**). The conditions of the reduction are difficult to control so that unreduced bromo ester **7** is sometimes recovered along with a product of further reduction, cyclobutylmethanol (**8**), and small amounts of cyclobutanecarboxaldehyde (**9**). Bromohydrin **1**, purified by vapor phase chromatography, is clearly different from bromohydrin **2** in spectral properties. The former's structure is certain from its method of synthesis as well as by its facile loss of hydrogen bromide to give cyclobutanecarboxaldehyde (**9**).[4]



Further confirmation of the correct assignment of structure is obtained by a comparison of the nmr spectra of the bromohydrins and their respective acetates. The exocylic methylene group of **2** appears as a singlet at δ 3.63, while the acetate derived from it shows this same absorption at δ 3.93, corresponding to a downfield shift of δ 0.30 from the parent alcohol. On the other hand, in bromohydrin **1** the exocyclic methylene appears as a singlet at δ 3.84, and the acetate's corresponding absorption comes at δ 4.40, a downfield shift of δ 0.56 from the parent alcohol. The δ 0.56 value for the α-acylation shift of **1** is in the proper range for a primary

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