The Ozonolysis of Tetrahydrochromans. Formation of Glycols and Normal Ozonolysis Products[1]

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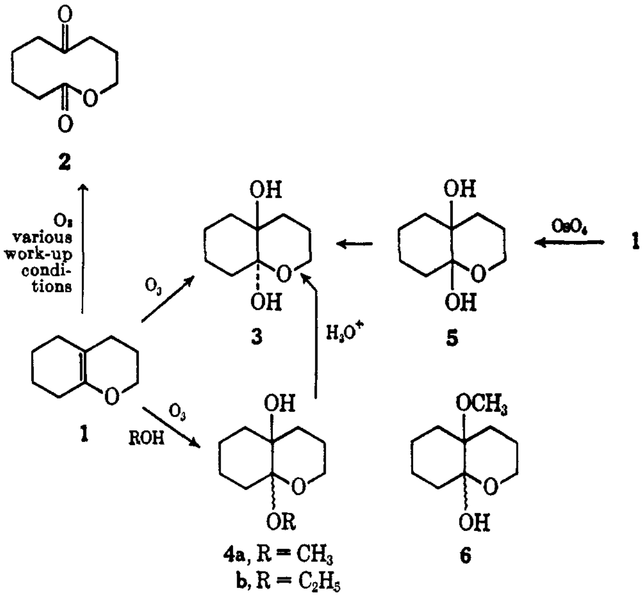
The ozonolysis of tetrahydrochromans followed by work-up with zinc and acetic acid gives varying amounts of 6-ketononanolides, the expected product, and *trans*-9,10-dihydroxyhexahydrochromans, depending on reaction conditions. Ozonolysis in methanol gives 9-methoxy-10-hydroxyhexahydrochroman as the principal product. It is postulated that ozonolysis of enol ethers such as tetrahydrochromans can give either ozonides and/or peroxidic products which are converted into the expected dicarbonyl products or epoxy ethers which are solvolyzed to give dihydroxy or alkoxyhydroxy ethers. Electronic factors leading to epoxy ether formation in ozonolysis and the problem of the assignment of stereochemistry to the isolated dihydroxy and alkoxyhydroxy ethers are discussed.

It has been suggested by Bailey and Lane[4] that the interaction of ozone with olefins can involve two distinct and competing processes proceeding from the formation of a π complex: (a) a concerted 1,3-dipolar cycloaddition of ozone which leads to the formation of an initial ozonide (a 1,2,3-trioxolane or "molozonide") which is converted to a "normal" ozonide (1,2,4-trioxolane) and derived normal ozonolysis products, and (b) conversion to a σ complex which loses molecular oxygen to give an epoxide and its derived products.

Epoxide formation has been observed in the ozonolysis of olefins which are substituted by bulky groups[4-6] and an argument based on steric hindrance to 1,3-dipolar addition of ozone has been advanced.[4] The "electrophilic trend" in the rates of ozone attack on olefins has been reemphasized recently[7] and it has been suggested that epoxide formation and related oxygen-transfer reactions are related to the ease of formation of stable carbonium ions.[4,7]

We now report that the ozonolysis of tetrahydrochromans such as 1[8,9] can lead to the normal ozonolysis products, 6-ketononanolides 2, and also to several products which can be rationalized as arising from epoxy ether intermediates: *trans*-dihydroxy ethers 3 and alkoxyhydroxy ethers 4 (Scheme I).

SCHEME I



Results

Table I summarizes our results on the ozonolysis of 1. Ozonolysis of 1 at −78° (Dry Ice–acetone) or at room temperature followed by rapid reductive work-up in acid (runs 1–3) gives 2 as the major product (54–70%) as well as small yields of 9,10-dihydroxyhexahydrochroman 3. These reactions were analyzed *via* gas chromatography on crude mixtures which were silanized.[10] The glycol 3 has been previously obtained by us in the treatment of 1 with moist perphthalic acid[8] or with osmium tetroxide followed by a reductive work-up with sulfite. The latter reaction presumably first gives the *cis*-glycol 5 which is readily isomerized to the *trans* isomer 3 at its anomeric center.[11] We have previously shown that 3 and the related 11 are most likely *trans* substituted.[9]

Runs 1–3 represent the best conditions for converting 1 to 2 by ozonolysis. Other runs (4–6) were unsuccessful. The best yield of glycol 3 (run 8) was reproducibly obtained by a 0° reductive work-up of a low-temperature ozonolysis mixture which had been allowed to remain at −78° for 12 hr.[12] Ozonolysis of 1 in methanol with a trimethyl phosphite work-up gave 9-methoxy-10-hydroxyhexahydrochroman (4a) (23% isolated, 46% by vpc). In order to clarify the origin of the methoxy group in 4a, 1 was ozonized in methanol with no work-up (run 10) to give 4a (34%). Thus 4a can be formed without the presence of trimethyl phosphite. A similar reaction of 1 in ethanol with triethyl phosphite work-up gave 4b (run 11). As a check, treatment of 1 with oxygen gave no reaction. The structure of 4a follows from its facile conversion to 3 with dilute acetic acid, another example of rapid solvolysis at an anomeric center. If 4a had the positions of the hydroxy and

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[3] Taken from the Ph.D. Thesis of R. D. Rapp, Lehigh University, 1967.

[4] P. S. Bailey and A. G. Lane, *J. Amer. Chem. Soc.*, **89**, 4473 (1967), and cited references; R. W. Murray, *Accounts Chem. Res.*, **1**, 313 (1968).

[5] P. D. Bartlett and M. Stiles, *J. Amer. Chem. Soc.*, **77**, 2806 (1955).

[6] P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

[7] D. G. Williamson and R. J. Cvetanovic, *J. Amer. Chem. Soc.*, **90**, 4248 (1968).

[8] I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966).

[9] I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *ibid.*, **33**, 2013 (1968).

[10] C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

[11] For related arguments on anomeric center reactions, see ref 9.

[12] First performed by George Gonis, Lehigh University.

TABLE I
THE OZONOLYSIS OF TETRAHYDROCHROMAN

Run No.	Reaction conditions	Reducing agent	Reduction temp, °C	Yields, % Keto-lactone	Dihydroxy ether	Alkoxyhydroxy ether	Other
1[a]	Methylene chloride, 25°	Zn-HOAc	Reflux	70	3		
2[a]	Methylene chloride, −78°	Zn-HOAc	−78	54	6		
3[a]	Methylene chloride, −78°	Zn-HOAc	Reflux	68	4		
4	Ether, −78°	BuMgI	−78				*c*
5	*n*-Hexane, −78°	$(CH_3O)_3P$	−78				*c*
6	Methanol, −78°	Ph_3P	−78				Polymer
7[b]	Methylene chloride, −78°; 12 hr at −78°	Zn-HOAc	25		14.5		
8[b]	Methylene chloride, −78°; 12 hr at −78°	Zn-HOAc	0		39		
9	Methanol, −78°	$(CH_3O)_3P$	−78	15[a]	3[a]	23,[b] 46[a] (**4a**)	
10[a]	Methanol, −78°	CH_3OH	25			34 (**4a**)	
11[a]	Ethanol, −78°	$(C_2H_5O)_3P$	−78			11 (**4b**)	

[a] Yields by vpc on silanized reaction mixtures. [b] Isolable yields. [c] Undefined products.

TABLE II
THE OZONOLYSIS OF SUBSTITUTED TETRAHYDROCHROMANS

Run no.	Reaction conditions	Reducing agent	Reduction Temp, °C	Yields, %[a] Keto-lactone	Dihydroxy ether	Alkoxy hydroxy ethe
1	Methylene chloride, −78°, on **7**	1. HOAc 2. Zn-HOAc	Reflux	53		
2	Methylene chloride, −78°, on **7**	1. HOAc 2. Zn-HOAc	Reflux	56		
3	Methylene chloride, −78°, on **8**	Zn-HOAc	Reflux	4	20 (11)	
4	Methanol, −78°, on **8**	$(CH_3O)_3P$	−78	*b*	*b*	*c*

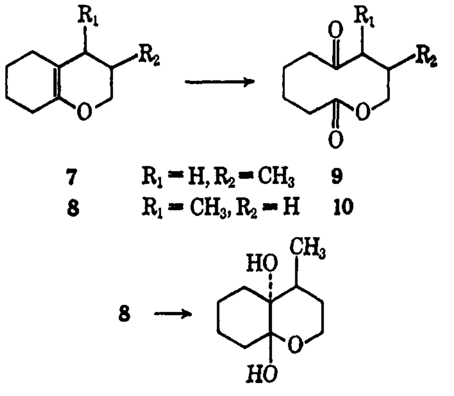
[a] Isolable yields. [b] Present by tlc. [c] Small yield (*ca.* 6%) present; nmr (CCl_4) consistent with presumed structure but not conclusive; could not be purified to analytical purity.

methoxy groups reversed, as in **6**, no conversion to **3** would be expected with dilute acid.

The assignment of the stereochemistry of **4a** presents difficulty. Infrared studies suggest that **4a** is intramolecularly hydrogen bonded (see Experimental Section) with ν_{OH} 3600 cm^{-1} at 0.005 *M* in carbon tetrachloride. While such bonding is only possible between the hydroxy and methoxy groups in the *cis* isomer, it is also possible between the hydroxyl and the ring oxygen in both the *cis* and *trans* isomers.[13] The observed ν_{OH} and $\Delta\nu_{OH}$ (from cyclohexanol) is such that we cannot distinguish between these types of intramolecular hydrogen bonding for **4a**. Thus our stereochemical assignment must remain in doubt. The actual stereochemistry of **4a** may not be very informative mechanistically, in any case, since the methoxyl in **4a** is at an anomeric center. Thus the relative stereochemistry of **4a** as isolated may not be the same as that of the form initially obtained in the ozonolysis of tetrahydrochroman.

The ozonolysis of 3-methyltetrahydrochroman **7** and the 4-methyl isomer **8** are given in Table II. Reasonable yields of 8-methyl- and 7-methyl-6-ketononanolides **9** and **10** were obtained if the initial ozonolysis mixtures were treated with acetic acid at reflux before reductive work-up with zinc–acetic acid (Scheme II). Omission of the acetic acid treatment in the ozonolysis of **7** resulted in a low yield of **9** (run 3).

SCHEME II



7 $R_1 = H, R_2 = CH_3$ **9**
8 $R_1 = CH_3, R_2 = H$ **10**
8 → **11**

Discussion

Our results suggest that the ozonolysis of tetrahydrochromans may occur *via* two pathways. The normal pathway, leading to 6-ketononanolides, can be visualized as in Scheme III. It may involve the formation of the "normal" ozonide **15** and, more probably, the dimeric ketoperoxide (**17** and isomers) as is found in the ozonolysis of 9,10-decalin and other tetrasubstituted olefins.[6,14] The alternate pathway may involve epoxy ether formation. We suggest that epoxide formation may be important in tetrahydrochroman ozonolysis

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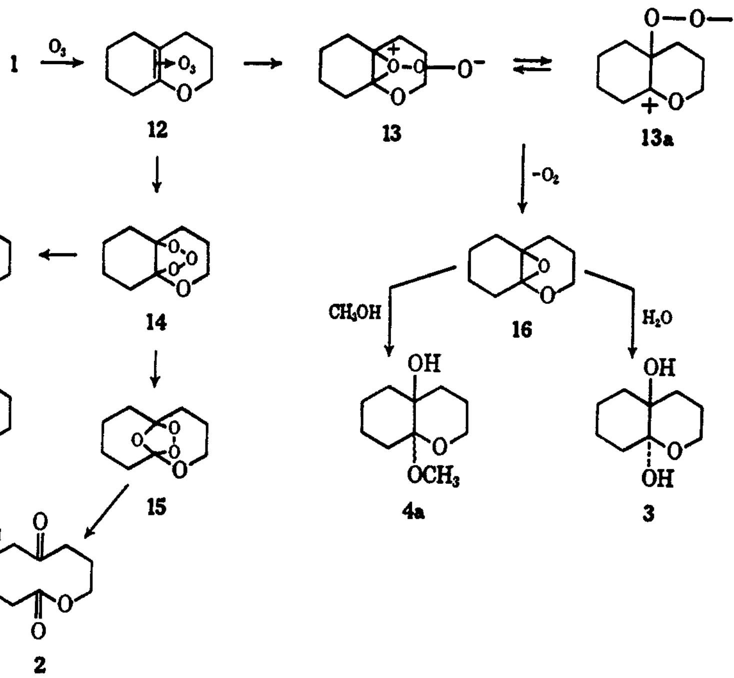
[13] M. Tichy, *Advan. Org. Chem.*, **5**, 115 (1965).

[14] R. Criegee, *Ann.*, **583**, 1 (1953), and references therein.

SCHEME III



because of the stabilization of positive charge in intermediates such as **13a** by the ring oxygen.[15] The epoxy ether **16** is not isolable, in keeping with the known high reactivity of epoxy ethers toward nucleophiles.[16] Thus conversion of **16** to **3** with water or to **4a** with methanol should occur readily.[17]

Our data suggest the following possibilities. Ozonolysis of **1** in the polar solvent methanol may encourage formation of the dipolar species **13** and/or **13a** with the resultant production of **16** and then **4a**.[18] Reaction in less polar solvents, such as methylene chloride, may allow the formation of molozonide **14** to predominate, albeit slowly. It is clear from our data that treatment of an ozonized mixture with acetic acid enhances ketolactone formation while formation of the glycol **3** is enhanced by "aging" the ozonized mixture before work-up. Our data is probably insufficient to fully explain these effects. We suggest, however, that the addition of acetic acid might cause protonation of **13**–**13a** and thereby slow down the formation of **4a** more than it influences the formation of **14** or **17**. This argument assumes that species such as **13** and/or **13a** are present after ozonolysis so that they can be influenced during work-up. This possibility is speculative and other factors which influence the formation of **2** *vs.* **3** may have to be considered. It has been suggested that the function of acetic acid is to make the reduction of species such as **17** more likely.[19] While this might explain the high yields of **2** in runs 1–3 (Table I), it does not explain the product differences noted in runs 7–11. It would appear that the initial competition between the formation of **16** and **14** (or **17**) is influenced by a number of factors including the nature of the solvent and the reaction conditions.

Since ozonolysis in methanol gives only a small amount of **2**, the difference due to the use of triphenylphosphine or triethyl phosphite in the subsequent work-up (runs 6,9) is not readily defined. It is of some interest that work-up with triphenylphosphine,[20] or butylmagnesium iodide,[21] both of which have been used in other ozonolysis work-ups, is totally unsuccessful in our work. In relation to our runs **4** and **5** we note that Criegee has previously found that the ozonolysis of tetrasubstituted olefins in nonpolar solvents (methyl chloride or petroleum ether) gives polymeric peroxides.[14]

Experimental Section

Gas chromatograms were recorded on a Varian Aerograph A-700 gas chromatograph employing stainless steel columns packed with 20% DEGS or 1–20% SE-30 on Chromosorb W as noted. Other instrumental and experimental techniques as well as the preparation of tetrahydrochromans have been previously described.[9]

General Ozonolysis Procedure.—A Welsbach T-23 ozonizer was used with 67-V potential on the primary coils and an oxygen pressure of 8 psi. The oxygen was dried by a potassium hydroxide tower before entering the ozonizer. Ozone concentration, determined by bubbling the gas stream through a 5% solution of aqueous potassium iodide for a measured period of time and titrating the liberated iodine with standard thiosulfate solution, was *ca.* 0.15 mmol/min. Ozonolysis was performed in a reaction flask followed by an after bubbler containing KI solution to detect ozone coming through the reaction flask. Ozone uptake was usually quantitative. The ozonizer was then turned off and oxygen was passed through the ozonizer and reaction flask for 15 min to remove excess ozone. The reduction of the ozonide thus formed was done as described below.

Silanization of Ozonolysis Reaction Mixtures.[10]—To a vial containing the reaction mixture resulting from ozonolysis work-

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[15] The structures **13** and **13a** may also be considered to be related to σ complexes. These have been recently emphasized in certain ozonolyses: P. R. Story, R. W. Murray, and R. D. Youssefyeh, *J. Amer. Chem. Soc.*, **88**, 3144 (1966).

[16] C. L. Stevens and J. Tazuma, *ibid.*, **76**, 715 (1954), and references cited therein.

[17] The possibility that conversion of **2** into **3** occurs under reductive work-up was eliminated *via* a control experiment which showed that the ketolactone **2** is recovered (92%) after treatment with zinc and acetic acid in CH_2Cl_2 at reflux.

[18] It is possible that **4a** is directly formed from **13**–**13a**, as is suggested by Professor Robert Murray.

[19] Suggested by a referee.

[20] L. Horner in "Newer Methods of Preparative Organic Chemistry," Vol. 2, W. Foerst, Ed., Academic Press, New York, N. Y., 1963, pp 163–212.

[21] F. L. Greenwood, *J. Org. Chem.*, **29**, 1321 (1964).

up (10 mg) in dry pyridine (0.20 ml) was added hexamethyldisilazane (0.20 ml) and trimethylchlorosilane (0.10 ml). The capped vial was shaken for 30 sec, the precipitated salt was allowed to settle, and a sample (15 μl) of the supernatant liquid was used in vpc analysis on a 1% SE-30 column. The relative amounts of various components present was estimated by the use of calibration curves for the pure components.

The Ozonolysis of Tetrahydrochroman 1. A. Reduction with Trimethyl Phosphite in Methanol.—The ozonolysis of 1 (2.76 g, 0.020 mol) in methanol (100 ml) at −78° (Dry Ice–acetone) by the above procedure (run 9, Table I) was followed by the addition of trimethyl phosphite (3.97 g, 0.0320 mol) at −78° over a 15-min period. The mixture was stirred an additional 30 min before being brought to room temperature. Removal of methanol *in vacuo*, addition of ether, washing the ether solution with water, drying, and removal of solvent gave an oil (2.30 g). The oil deposited 9-methoxy-10-hydroxyhexahydrochroman (**4a**) (0.85 g, 0.0046 mol, 23%): mp 86.5–87.0°; nmr ($CDCl_3$), τ 6.45 (m, 2, CH_2O), 6.82 (s, 3, OCH_3), 7.61 (s, 1, OH), 8.0 (m, 2, CH_2CH_2OH), and 8.45 (m, 10, CH_2); mass spectrum (70 eV),[22] *m/e* 186 (M^+) (calcd 186), 168 ($M - H_2O$), 154 ($M - CH_3OH$).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.60; H, 9.83.

In another run the oil resulting from the above work-up was silanized and analyzed by vpc at 150° to contain **4a** (1.7 g, 0.0091 mol, 46%), **2** (0.5 g, 0.003 mol, 15%), and **3** (0.1 g, 0.0006 mol, 3%). A similar reaction in ethanol with triethyl phosphite–ethanol work-up gave the presumed **4b** (11%), mp 108–113°, which had **3** as a persistent impurity (by vpc) and could not be prepared analytically pure by recrystallization or sublimation (run 11).

B. In Methanol.—Similar ozonolysis in methanol (100 ml) at −78° and removal of the solvent *in vacuo* at room temperature gave an oil which slowly deposited **4a** (1.27 g, 0.0068 mol, 34%), mp 80–84°, mmp 84–85° with the above sample (run 10).

C. Reduction with Zinc–Acetic Acid at 0°.—Ozonolysis of 1 (0.020 mole) in methylene chloride (100 ml) at −78° was followed by storage at −78° for 12 hr. The mixture was then brought to 0°; zinc dust (3.9 g, 0.059 g-atom) and acetic acid (8.3 ml) were added. The mixture was stirred for 2 hr, the zinc and the solvent were removed by filtration and evaporation, respectively, and the residue was dissolved in hot carbon tetrachloride. Upon cooling, **3** (1.33 g, 0.0077 mol, 39%), mp 112–121° and mmp 122–124° with genuine sample of mp 125–127°, precipitated.

D. Reduction with Zinc–Acetic Acid at Other Temperatures.—Ozonolysis of 1 followed by addition of zinc–acetic acid at −78° for 2 hr gave a mixture which was brought to room temperature, filtered, washed with 2% potassium carbonate and water, dried, and evaporated to give an oil (2.04 g) which contained (vpc on a silanized sample) **2** and **3** (runs 1–3, 7, Table I). Ozonolysis at −78 or 30° followed by immediate work-up with zinc–acetic acid in methylene chloride at reflux (40°) gave **2** and **3** as shown in Table I.

E. Other reduction methods are indicated in Table I and were unsatisfactory for the conversion of 1 to 2 (runs 4–6).

The Ozonolysis of Substituted Tetrahydrochromans. A. Best Conditions.—Ozonolysis of **7** or **8** (0.020 mol) followed by addition of acetic acid (8.3 ml), a reflux period of 12 hr, addition of zinc dust (3.9 g, 0.059 g-atom), and a further reflux period of 36 hr gave **9**, bp 105–110° (0.15 mm), or **10**, bp 100–110° (0.1 mm), ir and nmr spectra identical with those of genuine samples[9] (Table II).

B. Formation of the Glycol 11 from 4-Methyltetrahydrochroman 8.—Ozonolysis of **8** at −78° was followed by bringing the reaction mixture to room temperature and the addition of zinc–acetic acid (amounts as in section A). The mixture was then heated at reflux overnight (work-up as in D above) to give 4-methyl-9,10-dihydroxyhexahydrochroman **11** (0.74 g, 0.0040 mol, 20%): mp 151–152°; ir (CCl_4), 3600 cm^{-1}.

Anal. Found for $C_{10}H_{18}O_3$: C, 64.60; H, 9.71.

Distillation of the residual oil gave **10** (0.16 g, 0.00087 mol, 4%), ir spectrum (neat) identical with that of genuine 7-methyl-6-ketononanolide.[9] Work-up on an ozonolysis of **8** in MeOH with $(CH_3O)_3P$ gave the results indicated in Table II, run 4.

Infrared Studies[23] on 4a and 11.—The model compound 2,5-dimethylcyclohexanol (1.0 *M* in CCl_4 in a 0.1-mm NaCl cell) showed a sharp band at 3620 (free OH) and a broad band at 3390 cm^{-1} (intermolecular H-bonded OH); a 0.1 *M* solution showed increased absorption at 3620 and none at 3390 cm^{-1}. A dilute solution of cyclohexanol (CCl_4) gave a sharp peak at 3630 cm^{-1} (lit.[24] 3625 cm^{-1} for free OH). Infrared spectra of *trans*-2-methoxy-1-cyclohexanol[25-27] taken at 1.0, 0.1, and 0.05 *M* concentrations (CCl_4) with cell path lengths of 0.1, 1.0, and 1.0 mm, respectively, gave, at 1.0 *M*, a broad band at 3480 and a sharp peak at 3600 cm^{-1} (equal intensity); at 0.1 *M*, 3480 (weak) and 3600 cm^{-1} (strong); at 0.05 *M*, only 3600 cm^{-1}. The 3600-cm^{-1} peak is the intramolecular H-bonded OH (lit.[28] 3594 cm^{-1}) while the 3480 peak is the intermolecular H-bonded OH.

Spectra of a saturated and a 1:10 saturated solution of **4a** (CCl_4) showed a sharp peak at 3600 and a broad band at 3510 cm^{-1}. On further dilution to 0.0077 and 0.005 *M* solutions, **4a** showed only the 3600-cm^{-1} peak. The 3510-cm^{-1} peak was assigned to an intermolecular H-bonded OH since it disappeared upon dilution.[18,24b] The 3600-cm^{-1} peak is probably due to an intramolecular H-bonded OH. Since both the *cis* and *trans* forms of **4a** can have intramolecular H-bonding (see Discussion) no stereochemical assignment could be made.

The stereochemistry of **11** was assigned the *trans* configuration as already published.[9]

The Hydrolysis of 9-Methoxy-10-hydroxyhexahydrochroman 4a to the Glycol 3.—A solution of **4a** (0.1 g) in methanol (10 ml), glacial acetic acid (0.5 ml), and water (3 ml) was kept at room temperature overnight and then heated at reflux for 3 hr. Analysis (tlc on silica gel using 25% MeOH–C_6H_6 for development) showed that **3** was mainly present with only a trace of starting material: product mp 115–120°, mmp 119–124° with a genuine sample of **3** of mp 121–125°.

The Reaction of Tetrahydrochroman with Osmium Tetroxide.—To a solution of **1** (0.136 g, 0.000983 mol) and pyridine (0.156 g, 0.00197 mol) in isooctane (15 ml) was added osmium tetroxide (0.250 g, 0.000983 mol) in isooctane (20 ml). A brown precipitate formed immediately. The reaction mixture was stirred at room temperature for 48 hr, and the precipitated osmate ester was collected, washed with isooctane, and hydrolyzed with sodium sulfite (25 g) in 50% aqueous ethanol (50 ml). After 30 min the reaction mixture was filtered and extracted with CH_2Cl_2, and the organic layer was dried and evaporated to give *trans*-9,10-dihydroxyhexahydrochroman (**3**), mp 126–127°, mmp 127–128° with genuine **3** of mp 125–127°; the ir of the product (Nujol mull) was identical with that of genuine **3**.

Registry No.—**1**, 7106-07-2; **4a**, 19689-90-8; **11**, 19685-08-6.

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[22] Kindly performed by David Baugher of PAR Associates on a modified CEC mass spectrometer Model 21-103C utilizing a Micro-Teck high-temperature inlet system.

[23] Determined on Beckman IR-8 and Perkin-Elmer 227 grating infrared spectrophotometers, using variable-thickness NaCl cells.

[24] (a) B. Casu, M. Reggiari, G. G. Gallo, and A. Viginani, *Tetrahedron*, **22**, 3061 (1966); (b) L. P. Kuhn, *J. Amer. Chem. Soc.*, **74**, 2492 (1952).

[25] Synthesized from cyclohexene oxide and sodium methoxide[26] (35%), bp 87–92° (13 mm), lit.[27] bp 72–73° (10 mm), or from cyclohexene oxide, methanol, and *p*-toluenesulfonic acid (52%), bp 94–96° (35 mm).

[26] P. Bedos and M. C. Moreau, *Compt. Rend.*, **183**, 750 (1926).

[27] S. Winstein and R. B. Henderson, *J. Amer. Chem. Soc.*, **65**, 2196 (1943).

[28] K. W. Buck, A. B. Foster, A. Labib, and J. M. Webber, *J. Chem. Soc.*, 2846 (1964).