pyridine. Removal of the acetic anhydride *in vacuo* gave 1.71 g of the acetates, easily separable on a Carbowax 20M gas chromatography column. Planimeter measurement of peak areas showed the two acetates to be present in a 56:44 ratio. The purified *endo* isomer **16b** showed λ_{max} 5.75 and 8.1 μ, $n^{25}D$ 1.4449, and nmr signals at τ 8.98 (1 H, doublet, J = 6.5), 8.80 (3 H, singlet), 7.96 (3 H, singlet), and 6.15 (2 H, doublet, J = 7).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.43; H, 9.63.

The *exo* isomer **17b** showed λ_{max} 5.76 and 8.11 μ, and nmr signals at 8.87 (3 H, singlet), ~8.9 (1 H), 7.96 (3 H, singlet), and 5.68 (2 H, doublet, J = 7.5).

Anal. Found: C, 71.90; H, 9.55.

1,5-*exo*-Dimethylbicyclo[2.1.1]hexane (19).—The acetate **17b** (196 mg), purified by preparative gas chromatography, was reduced with excess lithium aluminum hydride. The resultant alcohol was converted to the tosylate and reduced in the same manner as described for **16a** to 18.1 mg of gas chromatographically pure hydrocarbon **19**. This material showed a molecular weight of 110 by mass spectroscopy and nmr signals at τ 7.95 (1 H, doublet, J = 2 cps), 8.18 (1 H, broad), 8.41 (2 H, singlet), 8.48 (2 H, singlet), 8.96 (3 H, doublet, J = 6.5), 8.98 (3 H, singlet), and ~9.0 (1 H). Insufficient material could be recovered for microanalysis.

The Synthesis of 6-Ketononanolides from Chromans[1]

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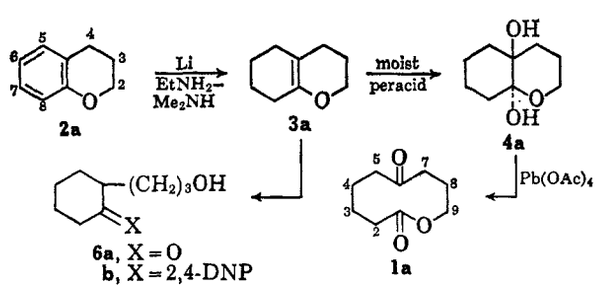
The reduction of chroman with excess lithium in ethylamine–dimethylamine (1:1 by volume) gives 5,6,7,8-tetrahydrochroman **3a**. Reaction of **3a** with perphthalic acid in moist ether gives a *trans* glycol **4a** which is cleaved with lead tetraacetate to give 6-ketononanolide **1a**. A direct conversion of **3a** to **1a** is obtained with an excess of *m*-chloroperbenzoic acid. The use of these methods in the synthesis of substituted 6-ketononanolides and the limitations of the *m*-chloroperbenzoic acid–olefin reactions are discussed.

It is of long-range interest to us to develop convenient syntheses of medium-ring keto lactones which are structurally related to the macrolide antibiotics. We wish to report the synthesis of the 6-ketononanolide system in this paper. The lithium–amine reduction of chromans **2a–2g** gives 5,6,7,8-tetrahydrochromans **3a–3g** which are then oxidized by various methods to give 6-ketononanolides **1a–1g**.

A series of chromans substituted in the aromatic ring was synthesized by the alkylation of the appropriate sodium phenoxide with 3-chloro-1-propanol to give the corresponding 3-phenoxy-1-propanol which was then cyclized by dehydration in boiling benzene with phosphorus pentoxide.[3] A 1.46:1 mixture of 7-methyl- and 5-methylchroman was prepared from *m*-cresol in this manner and then separated by repeated fractional distillation.[4] Impure 2-methylchroman **2f** was prepared according to a modification of the reaction of phenol with butadiene and 100% phosphoric acid as described by Bloch.[5] Since **2f** could not be entirely freed from low-boiling butadiene polymers, it was used in a purity of about 65% in the subsequent reactions.

The reduction of chroman **2a** with about 6.5 equiv of lithium in 1:1 (by volume) of dry ethylamine–dimethylamine gave **3a** in 85% yield based on a purity of 96% (by vpc). Two minor components were present (4% of the total material). The use of ethylamine–dimethylamine as a mixed solvent gave **3a** in higher purity and yield than did ethylamine alone or other amine combinations. Thus the yields and purity (by vpc) in the lithium–amine reduction of **2a** to **3a** were 68% (87% pure) from ethylamine, 22% (93% pure) from 1:1 ethylenediamine–morpholine, and 23% (100% pure) from ethylamine–diethylamine. The impurities noted in the ethylamine–dimethylamine reduction may be (a) one (or both) of the isomers of hexahydrochroman appearing as a single peak with shorter vpc retention time than for **3a** and (b) a double-bond isomer of **3a** with a longer vpc retention time. The identification of these minor components has not yet been carried out. The assignment of the less retentive minor peak to a hexahydrochroman is by analogy to the shorter vpc retention time for the decalin formed as a minor component in the lithium–amine reduction of naphthalene to 1,9- and 9,10-octalin.[6] The structure of **3a** was assigned on the basis of its analysis, nmr and infrared spectra (Experimental Section), and conversion to the 2,4-dinitrophenylhydrazone of 2-(3′-hydroxypropyl)cyclohexanone **6b** (58%).[7]



1a, unsubstituted	**2–4a**, unsubstituted
b, 4-methyl	**b**, 6-methyl
c, 2-methyl	**c**, 8-methyl
d, 5-methyl	**d**, 5-methyl
e, 3-methyl	**e**, 7-methyl
f, 9-methyl	**f**, 2-methyl
g, 2,5-dimethyl	**g**, 5,8-dimethyl
h, 3,5-dimethyl	**h**, 5,7-dimethyl

(1) This investigation was supported in part by Public Health Service Research Grant AI 06303 (to I. J. B.) from the National Institute of Allergy and Infectious Diseases. This is part III of the series, Medium Ring Compounds. Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, p 28S.

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(3) R. E. Rindfusz, P. M. Ginnings and V. L. Harnack, *J. Am. Chem. Soc.*, **42**, 157 (1920).

(4) Performed by S. S. Ho.

(5) (a) H. S. Bloch and H. E. Mammen, U. S. Patent 2,657,193 (Oct 21, 1953); *Chem. Abstr.*, **48**, 3724 (1954). (b) H. S. Bloch, personal communication.

(6) (a) G. Gonis, Lehigh University, unpublished results. (b) I. J. Borowitz and G. Gonis, *Tetrahedron Letters*, **No. 19**, 1151 (1964).

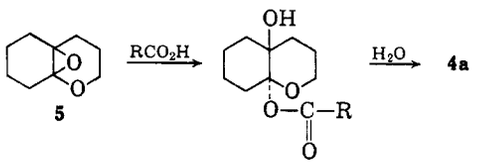
(7) H. Obara, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **82**, 60 (1961).

The reduction method is an application of the Benkeser reduction of aromatic rings to olefins.[8] Our reduction of chroman gives almost exclusively 5,6,7,8-tetrahydrochroman, the most substituted and presumably most stable of the possible enol ethers. This specificity is in fortunate contrast to the lithium–amine reduction of naphthalene which gives 9,10- and 1,9-octalin in about 4:1 ratio.[6a,8] A further point of interest is that in the chroman system reduction occurs and no observable carbon–oxygen cleavage. Anisole is known to give phenol (48%) under similar conditions.[8] Such ether cleavage is known to be slower for propyl (equivalent to the three alicyclic carbons in a chroman) than for methyl, which is indicative of initial fission to a carbanion.[9] In the chroman system such fission, if it occurs at all, must be a minor process. In the case of 5,7-dimethylchroman, at least, no phenol was found in the acidified residue after the tetrahydrochroman and other neutral products had been removed.[10] Chroman has previously been reported to be reduced with sodium in liquid ammonia to a dihydrochroman.[11]

The reduction of the substituted chromans went smoothly in high yields (73–81%) for most of the monomethyl cases, somewhat more slowly and in lower yield (56%) for 5,8-dimethylchroman **2g**, while with 5,7-dimethylchroman **2h** a mixture containing recovered **2h** (61%) and about 9% of the tetrahydrochroman was obtained even with a longer reaction time and larger excess of lithium. In relation to the previously mentioned difference in reduction of a chroman *vs.* an anisole, attempted reduction of 3,5-dimethylanisole gave only 3,5-dimethylphenol (92%). In contrast to the monomethyl results 6-*t*-butylchroman **7** reacted very slowly with lithium in ethylamine–dimethylamine to give four components including the desired 6-*t*-butyltetrahydrochroman **8** (about 18% of total).[12] The fact that **7** reduces very slowly is most probably due to a steric effect of the *t*-butyl group. It has recently been observed that 1,4-di-*t*-butylbenzene, which was known not to reduce with lithium–ammonia–ethanol,[13] does reduce with lithium in boiling ethylenediamine to a cyclohexene.[14] We did not try the latter solvent at the time of our work. Interestingly, Burgstahler has found that 1,2-di-*t*-butylbenzene reduces readily to a mixture of diene and olefin with lithium–ammonia–alcohol.[15] In this case the relief of strain of the two *t*-butyl groups in going from the aromatic system to the products overcomes any hindrance to reduction so that 1,2-di-*t*-butyl benzene is not a normal *t*-butyl case.

Tetrahydrochroman **3** has been previously synthesized *via* the cyclization and dehydration of 2-(3′-hydroxypropyl)cyclohexanone **6a**.[7]

The reaction of **3a** with 1 equiv of perphthalic acid in moist ether led directly to the 9,10-glycol **4a** (86%). The glycol, presumably *trans*, was characterized by its analysis and infrared, nmr, and mass spectrum. Reaction of **3a** with perphthalic acid (85.4% phthalic acid) in dry methylene chloride gave **4a** in 30% yield while perbenzoic acid in dry benzene gave 22% of **4a**. The glycol **4a** probably arises, in the moist ether reaction, by the opening of the initially formed epoxy ether **5** with water. In the reactions conducted in dried solvent **5** reacts with the carboxylic acid derived from the per acid used to give a hydroxy ester which would be expected to solvolyze readily with water during work-up to give **4a**.



Epoxy ethers are known to be readily opened by alcohols and acids and are not isolable unless stabilized by several phenyl groups.[16] Their rapid solvolytic reactions are due to the stabilization of an incipient positive charge on carbon by the adjacent oxygen. In our reactions neither epoxy ether, hydroxy ester, nor any meaningful products other than **4a** could be isolated. The further reaction of **4a** with lead tetraacetate in benzene led to 6-ketononanolide **1a** (83%; 61% from chroman). This cleavage reaction was used for several of the substituted glycols (Table I).

TABLE I

SYNTHESIS AND LEAD TETRAACETATE CLEAVAGE OF GLYCOLS TO 6-KETONONANOLIDES

Tetrahydrochroman[a] yield, %	Glycol yield, %	Keto lactone yield, %	Over-all[d] yield, %
Unsubstituted **3a**, 85	86	Unsubstituted **1a**, 83	72
3e (8-methyl), 80	33	**1c** (2-methyl), . .	41
3b (6-methyl), 81	83	**1b** (4-methyl), 52	43
3f (2-methyl),[b] *ca.* 73	85	**1f** (9-methyl), 77	65
3g (5,8-dimethyl), 59	*c*	**1g** (2,5-dimethyl)[c]	67

[a] Yields are for lithium–amine reduction of chromans. [b] The compounds **2f** and **3f** were used in an impure state. Yields are approximate. [c] The mixture of glycol and keto lactone obtained was allowed to react directly with lead tetraacetate. [d] Over-all yield from tetrahydrochroman.

It completed our first method for the construction of 10-membered keto lactones (over-all yields 33-61% from the corresponding chroman).

This two-step oxidation procedure of a tetrahydrochroman to a 6-ketononanolide was somewhat inconvenient and gave varying over-all yields. It was desirable to have a one-step high-yield method. Ozonolysis has proved to be complex and not valuable synthetically. Tetrahydrochroman **3a** can be ozonized to **1a** under certain conditions but the product is difficult to purify. Our ozonolysis studies on **3a** will be presented elsewhere.[17] The method that has been of most convenience to us is the one-step conversion of **3a** to **1a** with excess *m*-chloroperbenzoic acid (MCPBA).[18]

As is indicated in Table I the reaction of perphthalic acid in moist ether with 5,8-dimethyltetrahydrochro-

(8) (a) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1955). (b) R. A. Benkeser, personal communication.

(9) A. J. Birch, *J. Chem. Soc.*, 102 (1947).

(10) Performed by Stanley A. Kline.

(11) C. D. Hurd and G. L. Oliver, *J. Am. Chem. Soc.*, **81**, 2795 (1959).

(12) Compared with genuine **8** by vpc; the synthesis of **8** will be described elsewhere.

(13) P. Krapcho and A. Bothner-By, *ibid.*, **81**, 3658 (1959).

(14) R. D. Stolow and J. A. Ward, *J. Org. Chem.*, **31**, 965 (1966).

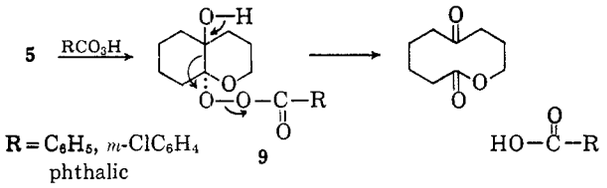
(15) A. W. Burgstahler, P. L. Chien and M. O. Abdel-Rahman, *J. Am. Chem. Soc.*, **86**, 5281 (1964).

(16) C. L. Stevens and J. Tazuma, *ibid.*, **76**, 715 (1954).

(17) R. Rapp, Lehigh University, unpublished results.

(18) Purchased in 80–85% purity from FMC Corp., Princeton, N. J.

man **3g** gave a mixture of glycol and keto lactone. We had also previously found that **3a** reacted with 1.1 equiv of MCPBA to produce **1a** directly in 17% yield.[6b] The mechanism that we then proposed and still invoke for the direct conversion of a tetrahydrochroman to a keto lactone with a peracid is illustrated for MCPBA. Initially formed **5** reacts with excess per acid to give a hydroxy per ester, most likely **9**, which then fragments to give **1a** and *m*-chlorobenzoic acid.



We later found that such a fragmentation had been previously observed and similarly rationalized in the reaction of an ethyl enol ether of a 20-keto steroid with perbenzoic acid to give a 17-keto steroid in 23% yield.[19] It was realized that for such a fragmentation process to predominate, it was necessary to have reaction of **5** with per acid, necessarily present in large excess, rather than with the corresponding acid.

Addition of 2.8 equiv of MCPBA to a solution of **3a** in methylene chloride gave **1a** (52%). Slow addition of **3a** to 3.0 equiv of MCPBA in methylene chloride followed by stirring at room temperature overnight gave **1a** in 92% yield. No glycol was obtained.

This latter procedure has become our best method for the conversion of tetrahydrochromans to 6-ketononanolides (Table II). The fragmentation reaction

TABLE II

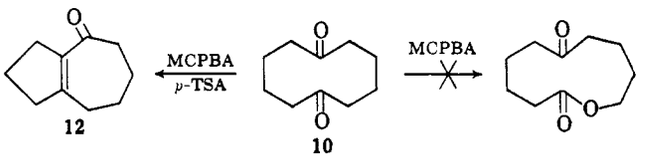
m-CHLOROPERBENZOIC ACID OXIDATION OF TETRAHYDROCHROMANS TO 6-KETONONANOLIDES

Tetrahydrochroman	6-Ketononanolide	Yield, %
Unsubstituted **3a**	Unsubstituted **1a**	92
3e (7-methyl)	**1e** (3-methyl)	46
3d (5-methyl)	**1d** (5-methyl)	50
3f (2-methyl)[a]	**1f** (9-methyl)	49
3b (6-methyl)	**1b** (4-methyl)	56

[a] Used in 85% purity.

is also observed with other peracids but gives **1a** in lower yield and purity. Thus addition of **3a** to 3 equiv of 45% perphthalic acid or perbenzoic acid gives **1a** in 60 and 25% yield, respectively. The advantage of MCPBA in our reaction system is at least partially due to the fact that *m*-chlorobenzoic acid precipitates as it forms and does not react further in competition with MCPBA. This solubility relationship is not so pronounced for benzoic or phthalic acid.

The favorable per acid/acid solubility ratio and the initial stability of MCPBA should make it an ideal reagent for the cleavage of enol ethers. The reaction will have several limitations with regard to broad application however. The only olefins that might be expected to react so are enol ethers. In other cases olefins are usually converted to epoxides which do not react further. Epoxidation reactions are, however, typically not done under conditions where the epoxide formed can then react with a large excess of peracid. We have reacted cyclohexene oxide and styrene oxide with excess MCPBA and have obtained complex mixtures not including simple aldehyde or ketonic products. Thus these epoxides probably open with MCPBA although the fragmentation reaction may not follow. Tetraphenylethylene when added to excess MCPBA gave 89% of the epoxide. This epoxide is too stabilized to react further. A further point arises in that in the cases that do fragment the resultant carbonyl compounds can react further with peracid to give Baeyer–Villiger esters or lactones. The medium ring systems such as **1a** are ideal products in the peracid reaction since they react very slowly with peracid.[20] We have found, for example, that cyclodecane-1,6-dione **10** gave no reaction with MCPBA after 31 days at room temperature or 48 hr at 43°. Higher temperature or addition of *p*-toluenesulfonic acid for catalytic effect led to the well-known transannular aldol reaction for **10** to give **12** and still no Baeyer–Villiger reaction.[6a]



We have used the MCPBA oxidation of cyclic enol ethers to synthesize 11- and 12-membered keto lactones.[21] It may be added that a much shorter reaction time (30 min) can be used for the enol ether oxidations in cases where Baeyer–Villiger oxidation of ketones to lactones is a serious problem.[22]

Oxidations of the cyclic enol ether system in N,N′-diacetylsolanocapsin have been carried out with potassium permanganate or chromic acid.[23] We attempted the oxidation of **3a** with potassium permanganate–periodic acid[24] but obtained no **1a**.

The keto lactones obtained are mainly liquids except for 6-ketononanolide **1a** which is a crystalline solid. 6-Ketononanolide **1a** has infrared absorption at 1735 and 1710 cm^{-1} for the lactone and ketone carbonyls, respectively. The ketone absorption is at higher frequency than that for cyclodecanone (1694 cm^{-1})[25] and may reflect ground-state dipole interaction of the carbonyls. The ultraviolet spectrum of **1a** has no special features and exhibits a broad maximum at 278 mμ (ε 18). The keto lactone forms a 2,4-dinitrophenylhydrazone with the lactone intact (1730 cm^{-1}), does not form a semicarbazone, and is recovered unreacted after overnight treatment with sodium borohydride in methanol. The lack of ketone reactivity is related to the known slow rate of reduction of simpler 10-membered ketones.[26] No abnormal rate acceleration

(19) B. Belleau and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 2816 (1952).

(20) S. L. Friess and P. E. Frankenburg, *ibid.*, **74**, 2679 (1952).

(21) I. J. Borowitz and G. J. Williams, *Tetrahedron Letters*, **No. 43**, 3813 (1965).

(22) I. J. Borowitz and G. J. Williams, First Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1966, p 119.

(23) K. Schreiber and H. Ripperger, *Ann.*, **655**, 114 (1962).

(24) R. U. Lemieux and E. Von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710 (1955).

(25) V. Prelog, *J. Chem. Soc.*, 420 (1950).

(26) M. Hanack, "Conformation Theory," Academic Press Inc., New York, N. Y., 1965, pp 164–171 and references therein.

due to possible dipole–dipole repulsion of the carbonyls was found. The ketononanolide system survives rapid sodium bicarbonate or sodium hydroxide treatment but slowly dissolves in 10% sodium hydroxide.

The keto lactones gave correct elemental analyses, molecular weights and characteristic mass spectral fragmentation patterns which will be discussed in a subsequent publication.

The nmr spectra of **1a** and **1c** include a triplet at τ 5.75 for the two A_2 protons on the C_9 methylene next to lactone oxygen. Thus **1c** exists in a conformation or conformations in which the presence of the C_2 methyl group does not cause the C_9 protons to be differentiated. With **1b**, **d**, and **e** the C_9 protons are not A_2 but AB. We have now synthesized the entire set of monomethyl 6-ketononanolides and are studying their nmr spectra in relationship to their conformations. This study will be published in a subsequent paper.

Experimental Section

Microanalyses were performed by Professor V. B. Fish of the Department of Chemistry, Lehigh University, Schwartzkopf Microanalytical Laboratories, Woodside, New York, and Galbraith Laboratories, Knoxville, Tennessee. Infrared spectra were recorded on a Beckman IR-8 infrared spectrophotometer. Vapor phase chromatograms were recorded on a Wilkens A-700 chromatograph using a 6 ft × 0.25 in. (o.d.) 20% diethyleneglycol succinate (DEGS) on Chromosorb P column unless otherwise noted. Nmr spectra were recorded on a Varian A-60A spectrometer with tetramethylsilane (τ10) as an internal standard. Melting points were taken on a "Mel-Temp" apparatus and are corrected while boiling points are uncorrected.

3-Hydroxypropyl Phenyl Ethers.—The procedure of Rindfusz[3] was used. **3′-Hydroxypropyl-3-methylphenyl ether** was prepared (61%) from *m*-cresol, bp 102–103° (0.2 mm), one peak (vpc). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.31; H, 9.16. **3′-Hydroxypropyl-2,5-dimethylphenyl ether** was prepared (65%) from 2,5-dimethylphenol, bp 152–154° (10 mm), 10% phenol impurity (vpc). Further treatment with base and redistillation gave a pure sample. *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95. Found: C, 73.09; H, 9.21. **3′-Hydroxypropyl-3,5-dimethylphenyl ether** was synthesized (43%) from 3,5-dimethylphenol, bp 111–119° (1–1.9 mm).

Chromans.—Chromans **2a**, **b**, and **c** were synthesized from the related hydroxypropyl phenyl ether[3] in 67, 60, and 81% yields; each compound was pure (vpc) and had an nmr spectrum consistent with its structure. **7-Methyl 2e** and **5-methylchroman 2d** were obtained as a 1.46:1 mixture (from vpc areas), bp 72–78° (0.3 mm), 68.3 g (0.46 mole, 78%), from the reaction of 3′-hydroxypropyl-3-methylphenyl ether (97.9 g, 0.59 mole) with phosphorus pentoxide (48.0 g, 0.336 mole) in boiling benzene for 3 hr. Fractional distillation of several combined runs (127 g) through a Todd Column employing a 45-cm helix packed column gave pure **7-methylchroman 2e**, 47.5 g (37% of input), bp 125–126.2° (26 mm), one peak (vpc). *Anal.* Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.88; H, 8.04. Further fractions were (a) 1:1 **2e–2d** (40 g, 31% of input), bp 128–132° (26 mm); (b) 1:4 **2e–2d** (32.5 g, 26% of input), bp 128–129.5° (19 mm). These fractions were redistilled using phenanthrene (0.25 of total weight of mixture) as a "chaser" and gave 16 g of pure **5-methylchroman 2d**, bp 56– 58° (75 mm). *Anal.* Found: C, 81.06; H, 8.36. The nmr spectrum (neat) of **2e** exhibits an AB quartet (2H) centered at τ 3.48 (C-5, C-6), singlet at τ 3.53 coincident with one line of the AB quartet (1H of C-8), triplet centered at τ 6.23 (2H of C-2), triplet centered at τ 7.62 (2H of C-4), singlet at τ 7.97 (3H of methyl), and a multiplet centered at τ 8.38 (2H of C-3). The nmr of **2d** (neat) exhibits a multiplet centered at τ 3.35 (3H of C-6,7,8), triplet centered at τ 6.18 (2H of C-2), distorted triplet centered at τ 7.72 (2H of C-4), singlet at τ 8.0 (3H of methyl), and a multiplet centered at τ 8.30 (2H of C-3). The former spectrum is clearly that of a 1,2,4-trisubstituted benzene, *i.e.* 7-methylchroman **2e**, so that the latter must be that of 5-methylchroman **2d**.

5,8-Dimethylchroman 2g was prepared in 86% cuder yield from 3′-hydroxypropyl-2,5-dimethylphenyl ether (some impurity by vpc), bp 114–116° (10 mm). An analytical sample was obtained by collection of the major vpc peak using a 0.375 in. × 20 ft 20% DEGS column at 198° with a helium flow rate of 200 ml/min. *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.13; H, 8.43. The nmr spectrum ($CDCl_3$) of **2g** exhibits an AB quartet centered at τ 3.30 (2 aromatic H), a triplet centered at τ 5.90 (2H of C-2), a triplet centered at τ 7.42 (2H of C-4), singlet at τ 7.85 (6H of methyls), and a multiplet centered at τ 8.0 (2H of C-3).

5,7-Dimethylchroman 2h was prepared in 74% yield from 3′-hydroxypropyl-3,5-dimethylphenyl ether, bp 85–86° (1.0 mm), colorless oil which crystallized at room temperature. *Anal.* Found: C, 81.36; H, 8.83.

2-Methylchroman 2f was prepared by the following modification of a procedure by Bloch and Mammen.[5] Butadiene was bubbled into a solution of phenol (200 g, 2.13 moles) in phosphoric acid (100%, 300 g) at 115° for 4 hr. The escaping butadiene was partially condensed with a Dry Ice condenser. Water (400 ml) was then added and the reaction mixture extracted with benzene (three 100-ml portions). The extract was washed with water (two 100-ml portions), 10% sodium hydroxide (to remove unreacted phenol), and water (three 100-ml portions), dried, and distilled to give 28 g of liquid, bp 105–112° (14 mm); vpc indicated 3 peaks with **2f** the major component (65% of total area, equivalent to 18 g of **2f**, 5.8% yield). Other runs using 90 and 80% phosphoric acid gave 39 g (65% pure) and 30 g (60% pure).

5,6,7,8-Tetrahydrochromans.—The following general procedure was used for reduction of the chromans and is illustrated for chroman. A mixture of freshly distilled (from lithium) ethylamine (100 ml) and dimethylamine (100 ml) was stirred with cut-up lithium wire (3.5 g, 0.5 g-atom) for 1 hr in a flask fitted with Dry Ice condensers. At this time the solution was usually colorless.[27] Chroman (10 g, 0.075 mole) was slowly added dropwise with stirring and the resultant mixture was stirred for about 9 hr. After about this time the mixture had turned blue and stirring was stopped. Excess lithium, which often had formed into one lump, was removed with tongs and solid ammonium chloride was added with stirring until the blue solution became colorless. The resulting gray solution was allowed to evaporate and if necessary it was taken to dryness by applying gentle heat (hot water bath) under water pump vacuum. Water (about 100–150 ml) was then added cautiously and the resulting mixture was extracted with ether (four to five 50-ml portions). The combined ether extracts were dried with magnesium sulfate, the solvent removed *in vacuo*, and the residue distilled to give a colorless liquid, 9.1 g, bp 68–72°, (10 mm); vpc showed a major peak with 96% of total area, a forepeak (3%), and an after peak (1%). The yield corresponds to 8.75 g or 84.5% of **3a**. *Anal.* Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.44; H, 10.42. The above procedure was used on substituted chromans with the following results.

8-Methyltetrahydrochroman, 80% yield, bp 78–82° (12 mm). *Anal.* Calcd for $C_{10}H_{16}O$: C, 78.91; H, 10.59. Found: C, 78.59; H, 11.07.

6-Methyltetrahydrochroman, 81% yield, bp 79–80° (12 mm). *Anal.* Found: C, 78.80; H, 10.64.

2-Methyltetrahydrochroman, about 73% yield based on weight of material of 80% purity, by vpc and nmr analysis, bp 49–53° (6 mm); used as is in further reactions since further purification was difficult.

7-Methyltetrahydrochroman, 47% yield, bp 104–106° (25 mm).[28] *Anal.* Found: C, 78.81; H, 10.60.

5-Methyltetrahydrochroman, 41% yield, bp 99–100° (24 mm).[28] *Anal.* Found: C, 78.77; H, 10.84.

5,8-Dimethyltetrahydrochroman, 56% after a reaction period of 11 hr, bp 70–75° (0.2 mm), one peak (vpc).[29] *Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.37; H, 11.04.

5,7-Dimethyltetrahydrochroman, about 9% of total amount of material (vpc areas) was formed along with mostly starting 5,7-dimethylchroman (61%), bp 70–126° (12 mm) after 12 hr; small amount purified.

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(27) Lithium in ethylamine alone formed a blue solution much more rapidly.

(28) These yields are minimal and may not represent the true values.

(29) The stereochemistry of the dimethyltetrahydrochromans will be discussed elsewhere.

6-*t*-Butyltetrahydrochroman was formed as follows. **6-*t*-Butylchroman**[30] (57 g, 0.30 mole) was added to lithium (15 g, 2.16 g-atoms) in ethylamine–dimethylamine (400 ml each). After 12 hr the mixture was worked up as described for **3a**, bp 79–116° (1.0 mm), and was 85% of one unknown component 11, 15% of two other components (vpc). This mixture was again treated with the lithium–amine combination as above for 28 hr and gave, after work-up, a mixture with bp 79–116° (1.0 mm), consisting of 50% of 11 and 50% of three other components including about 18% of **8**.[12] The nmr showed the absence of **7** and three *t*-butyl peaks.

Properties of Tetrahydrochroman.—The infrared spectrum (neat) of **3a** exhibits a peak at 1695 cm^{-1} (enol ether)[31] while the nmr spectrum ($CDCl_3$) exhibits a triplet centered at τ 6.05 (2H of C-2), a multiplet centered at τ 8.10 (8H of allylic C-4,5,8 and C-3) and a multiplet centered at τ 8.35 (4H of C-6,7).

2-(3′-Hydroxypropyl)cyclohexanone 2,4-dinitrophenylhydrazone 6b was prepared as follows. To **3a** (0.5 g, 0.0031 mole, 85% pure) in 95% ethanol–sulfuric acid was added excess 2,4-DNPH reagent (Brady's solution). A red 2,4-DNP formed, 0.7 g (67%), mp 126–128°, lit mp 126–127°.[7] *Anal.* Calcd for $C_{15}H_{20}N_4O_5$: C, 53.56; H, 5.99; N, 16.66. Found: C, 53.71; H, 6.04; N, 16.52. Both **3c** and **3g** did not form 2,4-DNP derivatives by this procedure.

Other Reductions to Tetrahydrochroman.—A. To ethylamine (freshly distilled from sodium) (200 ml) was added lithium (3.5 g, 0.5 g-atom) with stirring. After the mixture turned blue chroman (10 g, 0.075 mole) was added dropwise with stirring and the stirring was continued for 8 hr. Excess lithium was removed and work-up performed as before to give **3a**, 8.1 g, bp 78–81° (10 mm), 87% pure (vpc) with a forepeak (12–13%, possibly one or both hexahydrochroman isomers) and an after peak (1%), yield 7.0 g (68%).

B. Similar reaction with ethylenediamine (50 ml) and morpholine (150 ml) after 9 hr at reflux gave **3a**, 2.4 g, bp 75–78° (10 mm), 93% pure (vpc), yield 2.23 g (22%).

C. Similar reaction with ethylamine–diethylamine (1:1) gave **3a**, 23% (pure by vpc).

General Procedure for 1,6-Dihydroxy-2-oxabicyclo[4.4.0]-decanes.—To **3a** (20 g, 96% pure, 0.139 mole) in diethyl ether (75 ml), cooled in an ice bath, was added monoperphthalic acid[32] (30 g, 0.15 mole) in moist ether (500 ml), dropwise with stirring. After 20 hr additional perphthalic acid (7 g, 0.04 mole, in 100 ml of ether) was added. After several hr an excess of peracid was present (shown by liberation of iodine from starch–iodide paper). The precipitated phthalic acid was filtered off, the residual solution washed repeatedly with saturated sodium bicarbonate solution and dried, and the solvent removed *in vacuo* to give solid **4a**, recrystallized from carbon tetrachloride: 20.5 g, 0.12 mole, 86%; mp 119–120°. The product **4a** showed OH absorption (3210 cm^{-1}) and its nmr spectrum ($CDCl_3$) showed a diffuse triplet at τ 5.8–6.6 (includes 2H of C-2), OH singlets at τ 7.4 and 7.95 (exchangeable with D_2O), and a methylene envelope at τ 8.6; molecular weight (mass spectral) *m/e* 172, peaks at 154, 136 corresponding to the loss of one and two molecules of water observed. *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36; active H (Zerewitinoff), 1.16 (2 OH). Found: C, 62.55; H, 9.30; active H, 1.07.

8-Methyl-9,10-dihydroxyhexahydrochroman was thus prepared, 33%, mp 124–125°. *Anal.* Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.42; H, 9.66.

6-Methyl-9,10-dihydroxyhexahydrochroman, 82.5%, mp 128–129°. *Anal.* Found: C, 64.57; H, 9.74.

2-Methyl-9,10-dihydroxyhexahydrochroman, 85%, mp 92–93°. *Anal.* Found: C, 64.61; H, 9.60.

Other Reactions Giving Glycol Formation. Perbenzoic Acid.—To a stirred solution of **3a** (96% pure, 10 g, 0.08 mole) in benzene (50 ml), perbenzoic acid[33] (11 g, 0.08 mole) in benzene (500 ml) was added dropwise. The solution was stirred at 30° for 15 hr, extracted with sodium bicarbonate (four 200-ml portions), and dried, and the solvent removed to leave a dark yellow solid. Recrystallization from 30–60° petroleum ether gave 2.6 g (22%) of **4a**, mp 117–119°. Distillation of the residue gave starting material (3.1 g, 31%).

Perphthalic Acid in Dry Solvent.—To a stirred suspension of monoperphthalic acid (71.2 g, 0.057 mole, 14.6% purity) in methylene chloride (100 ml) was added **3a** (2.76 g, 0.020 mole) in methylene chloride (25 ml) over 10 min.; stirring continued 16 hr. The mixture was filtered, washed with 7% potassium bicarbonate until the washings were basic, dried, evaporated *in vacuo* to give an oil which deposited **4a**, 1.01 g, 29.5% yield. The formation of **4a** in this system is probably due to the high concentration of phthalic acid present in the monoperphthalic acid used. A similar reaction using perphthalic acid of higher purity gave only keto lactone (see below). In these preparations of perphthalic acid dry peracid was obtained by evaporating an ether solution in a vacuum dessicator over concentrated sulfuric acid. Removal of solvent at room temperature or 0° gave 14.6% and 45.3% perphthalic acid, respectively. The per acid was then dissolved in methylene chloride.

Lead Tetraacetate Cleavage of Glycols to 6-Ketononanolides.—To a suspension of **4a** (6 g, 0.035 mole) in dry benzene (150 ml) was added lead tetraacetate[34] (22 g, 0.05 mole) with stirring. After 3 hr at 28° glycerine was added and the solution gently warmed. Lead acetate was filtered off and washed with benzene; the washing was combined with the benzene solution which was dried and evaporated *in vacuo* to give **1a** as a white crystalline solid (4.9 g, 83%), mp 62–64°, 68–69° (after recrystallization from carbon tetrachloride). **6-Ketononanolide 1a** exhibited infrared carbonyl absorption (CCl_4) at 1735, 1710 cm^{-1}; and the nmr ($CDCl_3$) spectrum gave a triplet centered at τ 5.75 (2H of C-8), multiplet centered at τ 7.68 (8H of C-2,5,6,7), and a multiplet centered at τ 8.20 (4H of C-3,4). *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29; mol wt, 170.2. Found: C, 63.60; H, 8.08; mol wt (ebulliscopic and mass spectral), 170.

6-Ketononanolide 2,4-Dinitrophenylhydrazone.—To a solution of **1a** (0.2 g, 0.0012 mole) in 95% ethanol (10 ml) was added an excess of 2,4-DNPH (Brady's solution). After a few minutes a yellow 2,4-DNP formed, 0.40 g (94%), mp 208–210° (after recrystallization, twice from ethyl acetate and once from ethanol), infrared (CCl_4) at 1730 cm^{-1}. *Anal.* Calcd for $C_{15}H_{18}N_4O_6$: C, 51.42; H, 5.18; N, 15.99. Found: C, 51.57; H, 5.43; N, 15.80.

4-Methyl-6-Ketononanolide.—Treatment of **4b** with $Pb(OAc)_4$ gave **1b**, 52%, bp 126° (0.6 mm). *Anal.* Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.27; H, 9.13.

2-Methyl-6-Ketononanolide.—Similarly **4c** gave **1c** but in impure condition; a 2,4-DNP was prepared from this crude **1c** (see below). For pure **1c** it was best to prepare **4c** and cleave it without purification. This gave **1c**, 41% over-all yield from **3c**, bp 92–93° (0.6 mm). *Anal.* Found: C, 65.36; H, 9.06.

The **2,4-dinitrophenylhydrazone** of **1c** was prepared (37%), mp 182–183° (from ethyl acetate). *Anal.* Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.76; H, 5.69; N, 15.49.

9-Methyl-6-Ketononanolide.—Similarly **4f** gave **1f**, 76.5%, bp 83° (0.2 mm), mp (from petroleum ether) 37–37.5°. *Anal.* Found: C, 65.25; H, 8.77.

2,5-Dimethyl-6-ketononanolide.—The reaction of **4g** (18 g, 0.11 mole) with perphthalic acid (25 g, 0.136 mole) as before led to a mixture of glycol and keto lactone, part of which was directly treated with lead tetraacetate to give **1g**, 67% over-all yield from **4g**, bp 95° (0.7 mm). *Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.66; H, 9.11. Found: C, 66.78; H, 9.26.

Inverse Addition to Tetrahydrochromans of MCPBA.—The following procedure for the conversion of **3a** to **1a** serves as a generalized synthesis. Tetrahydrochroman **3a** (4.14 g, 0.30 moles) in methylene chloride (25 ml) was added slowly to MCPBA[18] (85% pure, 15.48 g, about 0.09 mole) suspended in methylene chloride (100 ml) at room temperature. The addition was made in about 40 min, gave an exothermic reaction, and was followed by stirring for 16 hr. During the course of the reaction MCPBA dissolved and then *m*-chlorobenzoic acid (MCBA) precipitated. This was then filtered off, the resulting solution was washed with 7% sodium bicarbonate (two 50-ml portions), water (50 ml), and dried; the solvent was removed on a rotary evaporator *in vacuo* to give crude solid (7.5 g) which was dissolved in methylene chloride and reprecipitated with 30–60° petroleum ether to give solid **1a**, mp 57–62° (4.7 g, 92%). Sublimation at bath temperature 50° (0.1 mm) gave **1a**, mp 64–70°,

(30) I. J. Borowitz and G. J. Williams, *J. Org. Chem.*, **31**, 603 (1966).

(31) A. F. Thomas and M. Stoll, *Chem. Ind.* (London), 1491 (1963).

(32) H. Bohme, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y. 1955, p 619.

(33) G. Braun, ref 32, Coll. Vol. I, 1941, p 431.

(34) This was purchased from Matheson Coleman and Bell, East Rutherford, N. J.

67%. The substituted 6-ketononanolides were thus synthesized and purified by distillation.[35]

3-Methyl-6-Ketononanolide.—Treatment of **3e** by the above procedure gave **1e**, 46%, bp 114–116° (2 mm). *Anal.* Found: C, 65.39; H, 8.85.

5-Methyl-6-Ketononanolide.—Treatment of **3d** similarly gave **1d**, 50% crude, bp 92–94° (1 mm). *Anal.* Found: C, 65.20; H, 8.67.

Other Conversions of Tetrahydrochromans to Ketononanolides. Addition of MCPBA to 3a.—The addition of MCPBA (14.0 g, 0.081 moles) of **3a** (4.0 g, 0.029 moles) in methylene chloride, followed by stirring for 16 hr and the above-mentioned work-up gave a wet solid which yielded **1a** (2.34 g, 48%).

Addition of 3a to Perphthalic Acid.—To a stirred suspension of monoperphthalic acid (24.0 g, 0.060 mole, 45.3% purity) in methylene chloride (100 ml) was added **3a** (2.76 g, 0.020 mole) at room temperature. The addition was done dropwise, stirring was continued for 16 hr, and the reaction was worked up as for the above-mentioned perphthalic acid run to give **1a**, 2.04 g, 60%.

Addition of 3a to Perbenzoic Acid.—Perbenzoic acid was prepared from sodium methoxide and benzoyl peroxide[33] but was extracted with methylene chloride instead of chloroform. To a stirred solution of perbenzoic acid (0.0631 mole) in methylene chloride (140 ml) was added **3a** (2.76 g, 0.020 mole) at room temperature; stirring was continued for 16 hr; the reaction mixture was washed with 7% potassium carbonate, dried, and evaporated *in vacuo* to give an oil (3.40 g) which contained about 25% of **1a** (vpc). The 6-ketononanolide **1a** could not be crystallized out of the oil.

Other Reactions with MCPBA. Tetraphenylethylene.—A suspension of tetraphenylethylene (0.996 g, 0.0030 mole) in methylene chloride (15 ml) was added, with stirring, to a suspension of MCPBA (1.55 g, 0.0090 mole) in methylene chloride (10 ml) at room temperature. There was no evolution of heat and little precipitate formed. After 16 hr, the reaction mixture was filtered and worked up as for the oxidation of **3a** to give tetraphenylethylene oxide (0.929 g, 89%), mp (from ethanol) 209–210°, lit.[36] 204–205° (α form).

Cyclohexene Oxide.—Addition of cyclohexene oxide (2.94 g, 0.030 mole) in methylene chloride (25 ml) to MCPBA (5.16 g, 0.030 mole) in methylene chloride (100 ml) (no exothermic reaction) followed by work-up as for **3a** gave a mixture possibly containing adipic acid (tlc). *m*-Chlorobenzoic acid (1.3 g) was recovered from the basic extract. Similar reaction with **styrene oxide** gave *m*-chlorobenzoic acid, benzaldehyde in small amount (by odor and tlc comparison with genuine benzaldehyde, and other compounds in a complex mixture.

Attempted Reaction of Cyclodecane-1,6-dione with MCPBA.—Treatment of cyclodecane-1,6-dione[37] (0.003 mole) with MCPBA (0.003 mole) in methylene chloride at 28° for 24 hr or 45° for 48 hr gave only starting material. Initial addition of *p*-toluenesulfonic acid (0.05 g) followed by reaction at room temperature or at 45° led to dark liquids possibly containing the unsaturated ketone **12**. The latter ketone was obtained from a similar reaction in ether (λ_{max} 252 mμ) and converted to the 2,4-dinitrophenylhydrazone, mp 251–252°. *Anal.* Calcd for $C_{16}H_{18}N_4O_4$; C, 58.17; H, 5.49. Found: C, 58.04; H, 5.45.

Reaction of cyclodecane-1,6-dione with MCPBA at 61° (boiling chloroform) also gave **12**.

Attempted Oxidation of Tetrahydrochroman with Potassium Permanganate–Periodic Acid.—Reaction of **3a** (0.138 g, 0.001 mole) in dioxane (3 ml)–water (150 ml)–potassium carbonate (0.040 g) with a suspension of periodic acid dihydrate (0.447 g, 0.00196 mole)–potassium carbonate (0.135 g, 0.001 mole) in distilled water (20 ml) followed by addition of potassium permanganate (0.0053 g, 0.00003 mole) in water (20 ml) at room temperature and the usual work-up[24] led to no recognizable product, definitely no **1a**.

Attempted Reduction of 6-Ketononanolide with Sodium Borohydride.—To **1a** (0.35 g, 0.0021 mole) in methanol (20 ml) was added sodium borohydride (0.084 g, 0.0022 mole) in portions with stirring. After reaction at room temperature for 16 hr, the mixture was poured into water and extracted with methylene chloride to give unchanged **1a** (identical infrared spectrum).[4]

The Reactivity of 6-Ketononanolide with Base.—A solution of **1a** in methylene chloride or ether was washed several times with either 7% sodium bicarbonate or 10% sodium hydroxide to leave unreacted **1a** (at least 91% recovery in the latter case). When **1a** was allowed to be in contact with 10% sodium hydroxide, it slowly dissolved (about 1 hr) to give a yellow solution. Acidification of the solution gave an oil which had hydroxyl and carbonyl infrared absorption.

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(35) It was occasionally noticed that, after thorough removal of *m*-chlorobenzoic acid, distillation of the crude mixtures from the MCPBA reactions caused a slight exothermic reaction, and further formation of *m*-chlorobenzoic acid, possibly *via* further decomposition of the postulated per ester **9**. Although these distillations have been carried out without incident, the possible presence of per esters in these mixtures should assure their handling with caution!

(36) "Dictionary of Organic Compounds" Vol. I, J. R. A. Pollack and R. Stevens Ed., Oxford University Press, Fairlawn, N. J., 1965, p 368.

(37) Prepared from a mixture of 9, 10- and 1, 9-octalin according to S. Dev, *J. Indian Chem. Soc.*, **31**, 1 (1954).