The Synthesis of 6-Ketononanolides, 6- and 7-Ketodecanolides, and 7-Ketoundecanolide *via* Enamine Reactions[1]

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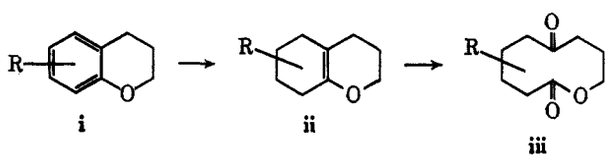
Alkylation of the pyrrolidine enamines of several cyclohexanones with 3-bromopropyl acetate gives the corresponding 2-(3′-acetoxypropyl)cyclohexanones. These keto esters are hydrolyzed to keto alcohols which are cyclized and dehydrated to tetrahydrochromans. Alkylation of pyrrolidinocyclohexene or pyrrolidinocycloheptene with 4-bromobutyl acetate gives the corresponding 2-(4′-acetoxybutyl)cycloalkanone which is converted similarly into a bicyclic enol ether. The tetrahydrochromans and other enol ethers are oxidized with *m*-chloroperbenzoic acid (MCPBA) to give the species named in the title. Further evidence toward the proposed mechanism of the MCPBA oxidations is given. The chromic acid oxidation of tetrahydrochromans to 6-ketononanolides is also presented. Possible extensions to larger ring keto lactones are discussed. The Michael addition of acrylate esters to enamines is extended to the synthesis of substituted 6-ketononanolides and 7-ketodecanolides.

The lithium–amine reduction of chromans i to tetrahydrochromans ii followed by oxidation with *m*-chloroperbenzoic acid (MCPBA) to 6-ketononanolides iii has been previously described by us.[4]



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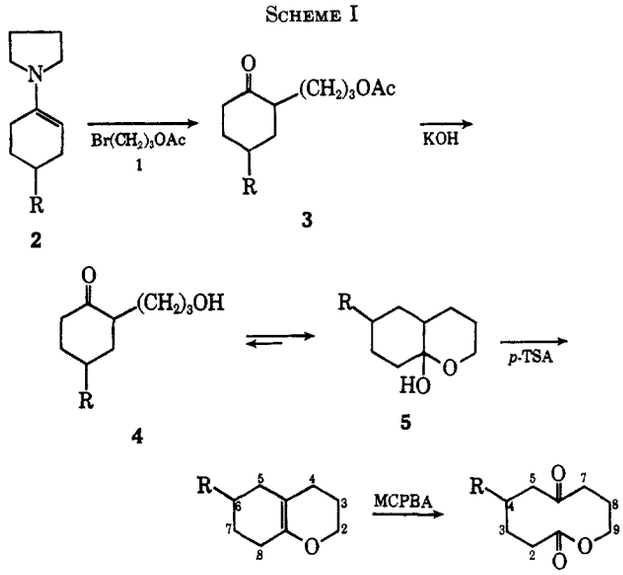
We now report syntheses of 6-ketononanolides, 6- and 7-ketodecanolides, and 7-ketoundecanolide based on the utilization of enamines.[5,6] These syntheses are not limited to preformed six-membered rings and are capable of variation of ring size and the introduction of stereochemical features at selected sites. They retain the facile cleavage of the double bond of a bicyclic enol ether with MCPBA.

Enamine Alkylations.—3-Bromopropyl acetate (**1**) was synthesized from 1,3-propanediol in reaction with acetyl bromide. Reaction with **2a** in toluene or acetonitrile gave 2-(3′-acetoxypropyl)cyclohexanone (**3a**) (Table I and Scheme I). The somewhat higher alkylation yield in acetonitrile (33%) than in toluene (20%) may indicate a polar solvent effect favoring C-alkylation, but no firm conclusion can be made until further data are available. Similar reaction of **1** with 4-*t*-butylcyclohexanone (**2b**) gave **3b**. Hydrolysis of the esters with ethanolic potassium hydroxide gave the corresponding 2-(3′-hydroxypropyl)cyclohexanones which were present mainly as their cyclized tautomers **5a** and **5b**. Distillation of **5a** or azeotropic dehydration of **5b** with *p*-toluenesulfonic acid in benzene[7] gave the tetrahydrochromans **6a** or **b** (Table I). The best over-all yield (21%) of **6a** from **2a** compares unfavorably with our 38% over-all yield of **6a** from phenol *via* the formation and subsequent reduction of chroman.[4] This method is however superior for the synthesis of 6-*t*-butyltetrahydrochroman (**6b**) since we had previously noted that the lithium–amine reduction of 6-*t*-butylchroman proceeds very slowly to give a mixture containing only *ca.* 18% of **6b**.

SCHEME I



2–**4,7a**, R = H
b, R = 4-*t*-butyl

5,6a, R = H
b, R = 6-*t*-butyl

In a similar manner the alkylation of **2a** with 4-bromobutyl acetate (**8**) (Scheme II), obtained from the reaction of tetrahydrofuran with acetyl bromide[8,9] and zinc chloride, in boiling toluene gave 2-(4′-acetoxybutyl)cyclohexanone (**9**) (21–42% yield). The further conversions of **9** into 2-oxabicyclo[5.4.0]undec-1-(7)-ene (**11**, 74% over-all from **9**) are given in Table I. Enol ether **11** had characteristic infrared absorption at 1680 cm^{-1}, related to the band at 1695 cm^{-1} found for **6**.[4]

(1) This investigation was supported by Public Health Service Research Grant AI 06303 and 07455 from the National Institute of Allergy and Infectious Diseases. This is part IV of the series, Medium Ring Compounds. Presented in part at the First Middle Atlantic Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1966, p 119.

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(3) Taken in part from the Ph.D. Thesis of R. Rapp, Lehigh University, 1967.

(4) (a) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966); (b) I. J. Borowitz and G. Gonis, *Tetrahedron Lett.*, 1151 (1964).

(5) G. Stork, A. Brizzolara, H. Landesman, and J. Szmuszkovicz, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(6) J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

(7) H. Obara, *Nippon Kagaku Zasshi*, **82**, 60 (1961).

(8) J. B. Cloke and F. J. Pilgrim, *J. Amer. Chem. Soc.*, **61**, 2667 (1939).

(9) J. S. Harding and L. N. Owen, *J. Chem. Soc.*, 1536 (1954).

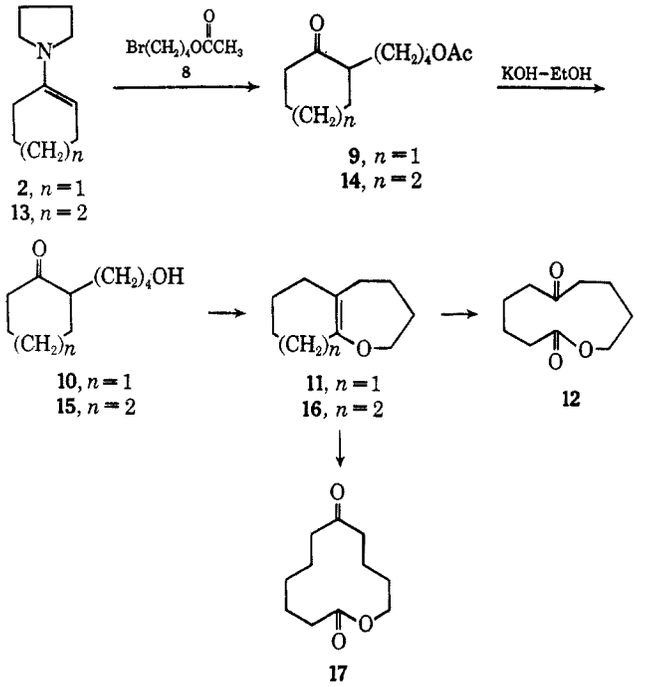
TABLE I

ACETOXYALKYL CYCLOALKANONES: SYNTHESIS, HYDROLYSIS, AND CONVERSION INTO TETRAHYDROCHROMANS

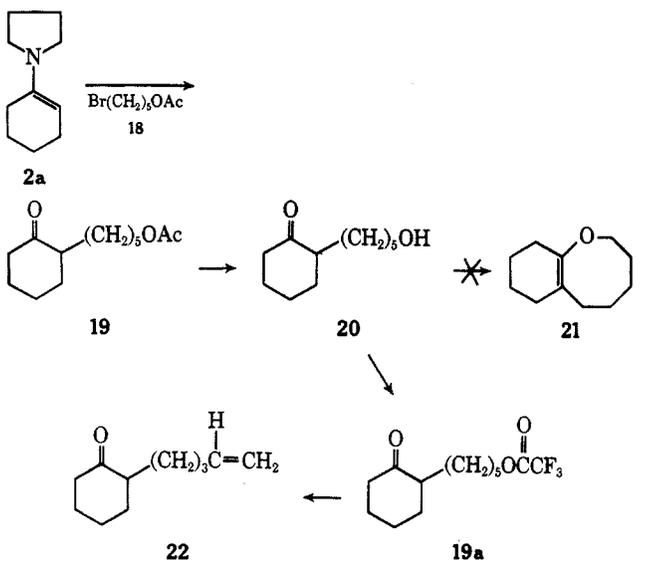
Acetoxyalkyl ketone	Yield, %	Hydroxy ketone yield, %	Enol ether yield, %	Over-all yield from enamine (**2** or **13**), %
2-(3′-Acetoxypropyl)cyclohexanone (**3a**)	20[a]			
	33[b]	...	**6a**, 64	13–21
4-*t*-Butyl-2-(3′-acetoxypropyl)-cyclohexanone **3b**	31–35	91	**6b**, 69.5	22–24
2-(4′-Acetoxybutyl)cyclohexanone (**9**)	21–42	...	**11**, 74	16–31
2-(4′-Acetoxybutyl)cycloheptanone (**14**)	28–48	...	**16**, 73	20–35

[a] Enamine alkylation in toluene. [b] Enamine alkylation in acetonitrile.

SCHEME II



SCHEME III



Pyrrolidinocycloheptene (**13**)[10] was alkylated similarly with **8** to give **14** (28–48%) and converted into the enol ether **16** (Table I).

In a further extension of the above-discussed method we have synthesized 2-(5′-hydroxypentyl)cyclohexanone (**19**) but have not yet succeeded in its ring closure. The alkylation of **2a** with 5-bromopentyl-acetate (**18**, Scheme III), obtained from the reaction of acetyl bromide with tetrahydropyran, gave **19** (11–20%) which was hydrolyzed as before to **20**. Attempted cyclization and dehydration of **20** to **21** with *p*-toluenesulfonic acid under various conditions gave either no reaction or some dehydration to what is probably the terminal olefin **22**.

Treatment of **20** with trifluoroacetic anhydride gave the trifluoroacetate **19a** and not the desired **21**.

Additions of Acrylates to Enamines.—Since enamine alkylations seldom occur in more than 40% yield,[5] we turned to the utilization of higher yield methods for the synthesis of bicyclic enol ethers. One of the best recent methods is that of Stork and Etheredge.[11] In this method Michael addition of an acrylate ester to a cyclohexanone enamine in alcohol solution allows the isolation of the adduct as the enamine in 70–91% yield. The enamine ester is then reduced with lithium aluminum hydride and hydrolyzed to give the corresponding 2-(3′-hydroxypropyl)cyclohexanone or cycloheptanone which is dehydrated to the bicyclic enol ether *via* either *p*-toluenesulfonic acid catalyzed azeotropic removal of water or distillation from potassium pyrosulfate (Table II). The sequence is illustrated in Scheme IV for the syntheses of the enol ethers **27** and **28** which are the precursors of 7-ketodecanolide (**29**) and 7-keto-8-methyldecanolide (**30**). The conversion of pyrrolidinocyclohexenes **2a–e** into the enamine adducts **31** (Table II) and then to tetrahydrochromans **6a–g** is also shown below and summarized in Table II.

MCPBA Oxidation of Tetrahydrochromans.—The tetrahydrochromans obtained by the above outlined sequence were oxidized by MCPBA as previously described[4] to yield the corresponding 6-ketononanolides in 50–67% yield (Table III). We have shown that addition of tetrahydrochroman **6a** to 3 equiv of MCPBA gives a much better yield of 6-ketononanolide **7a** than the addition of MCPBA to the enol ether. The latter is, of course, the usual procedure for the epoxidation of an olefin. In confirmation of the advantage of the inverse addition, the addition of MCPBA (3 equiv) to **6d** (8-methyl) gave **7d** in 37% yield (contrast with the 64% yield of **7d** *via* inverse addition in Table III).

We have previously postulated a fragmentation mechanism for this direct conversion of a tetrahydro-

(10) The reaction of pyrrolidine with cycloheptanone gave the corresponding enamine **13** in variable yields. Morpholine consistently gave good yields (*ca.* 63%) of morpholinocycloheptene. The latter enamine, however, gave no **14** upon reaction with **8**.

(11) (a) G. Stork and S. Etheredge, unpublished observations. (b) S. Etheredge, Ph.D. Thesis, Columbia University, 1965; *Dissertation Abstr.*, **26**, 4232 (1966).

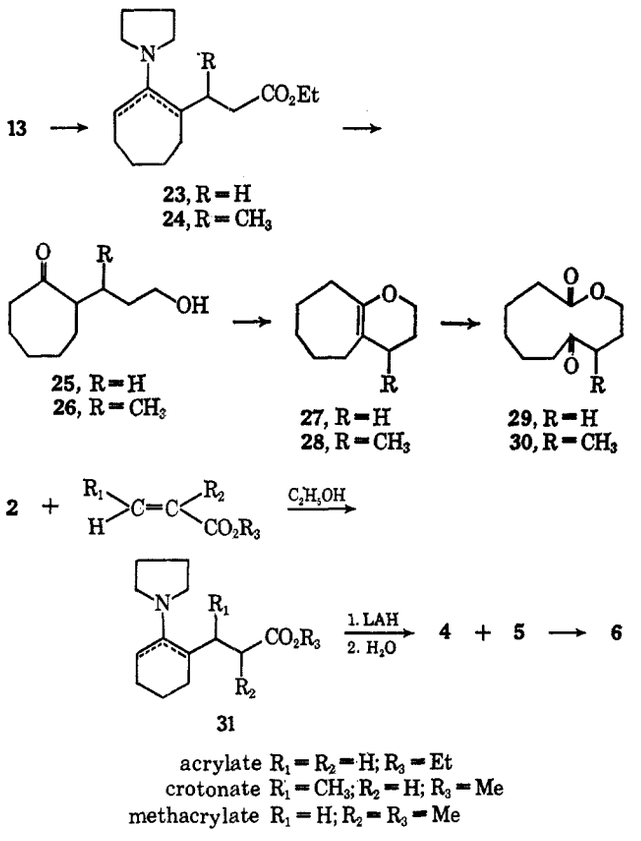
TABLE II

SYNTHESIS OF ENAMINE–ACRYLATE ADDUCTS AND CONVERSION INTO TETRAHYDROCHROMANS

Pyrrolidinocycloalkene	Acrylate	Enamine ester, % yield	Enol ether, % yield from enamine ester
Unsubstituted cyclohexene **2a**	$R_1 = R_2 = H$, $R_3 = Et$	**31a**, 91	**6a**, 70
4-*t*-Butyl **2b**	$R_3 = Et$	**31b**, 94	
4-Methyl **2c**	$R_3 = Et$	**31c**, 85[a]	6-Methyl **6c**, 81
2-Methyl **2d**	$R_3 = Et$	**31d**, 82	8-Methyl **6d**, 69
Unsubstituted **2a**	$R_1 = R_3 = Me$, $R_2 = H$ (crotonate)	**31e**, 83	4-Methyl **6e**, 70
Unsubstituted **2a**	$R_2 = R_3 = Me$, $R_1 = H$ (methacrylate)	**31f**, 89	3-Methyl **6f**, 74
3,5-Dimethyl **2e**	$R_1 = R_2 = H$, $R_3 = Et$	**31g**, 67	5,7-Dimethyl **6g**, 73
Unsubstituted cycloheptene **13**	Ethyl acrylate	**23**, 83.5	**27**, 32
13	Methyl crotonate	**24**, 72	**28**, 67

[a] Reduction to hydroxypropylcyclohexanone in 52% yield.

SCHEME IV



chroman into a keto lactone[4,12] *via* the intermediacy of an epoxy ether which is converted by MCPBA into a hydroxy per ester such as **32**. The postulated epoxy ether could react with MCPBA or the stronger acid, *m*-chlorobenzoic acid (MCBA).[12b]

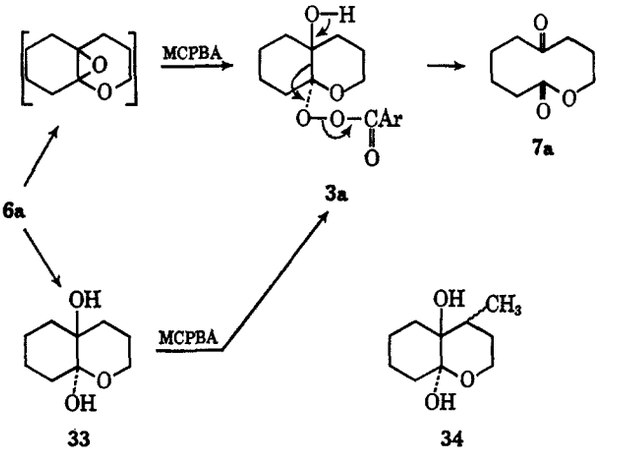
Fragmentation of **32** presumably occurs to give **7a**. We now find that treatment of the glycol **33**, previously obtained from **6a** with moist monoperphthalic acid,[4] with MCPBA also gives **7a** (70%). This novel reaction lends support to the postulated intermediacy of **32** in the formation of **7a** since the most reasonable pathway from **33** to **7a** also involves **32**.

TABLE III

m-CHLOROPERBENZOIC ACID OR CHROMIC ACID OXIDATION OF TETRAHYDROCHROMANS TO 6-KETONONANOLIDES

Tetrahydrochroman	6-Ketononanolide	Yield, % MCPBA	Yield, % Chromic acid
Unsubstituted **6a**	Unsubstituted **7a**	67[a]	...
3-Methyl **6f**	8-Methyl **7f**	50	71
4-Methyl **6e**	7-Methyl **7e**	56	68.5
8-Methyl **6d**	2-Methyl **7d**	64	47[b]
6-*t*-Butyl **6b**	4-*t*-Butyl **7b**	54–76	...
6-Methyl **6c**	4-Methyl **7c**	56[c]	47
5,7-Dimethyl **6g**	3,5-Dimethyl **7g**	51	...

[a] Crude yield, 92%. [b] Crude yield. [c] Previously reported: ref 4a.



The Stereochemistry of Glycol 33.—The postulated *trans* stereochemistry of **33** is enforced by its failure to give acetonide or cyclic carbonate derivatives (reactions of *cis*-glycols). The low solubility of **33** precluded infrared studies. However, the glycol **34** could be obtained from 4-methyltetrahydrochroman under certain ozonolysis conditions which also converted **6** into **7**.[13] Glycol **34** is more soluble in methylene chloride than is **33** and since it exhibited no hy-

(12) (a) A related cleavage of a steroidal enol ether of a 20-ketone to the 17-ketone was similarly rationalized: B. Belleau and T. F. Gallagher, *J. Amer. Chem. Soc.*, **74**, 2816 (1952). (b) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York, N. Y., 1967, p 135. (c) One advantage of MCPBA in our reaction systems is its greater solubility with respect to MCBA. The latter mainly precipitates as it forms and does not significantly react further. We have now found that MCPBA is five times more soluble than is MCBA in methylene chloride, the solvent used in our oxidations.

(13) R. Rapp, results to be published.

drogen bonding in the ir spectrum in dilute solution, it is assigned a *trans* stereochemistry.[14] Therefore **33** is presumably also *trans*. The transformation of *trans* **33** to *trans* **32** involves reaction at an anomeric center[15] which should occur *via* a carbonium ion type of solvolysis. Neighboring group participation by hydroxyl would then lead to the more stable *trans* product.

Oxidations of Other Enol Ethers.—The enol ether **11** was converted into 6-ketodecanolide (**12**) *via* two methods. Oxidation of **11** to the glycol[4a] followed by cleavage with lead tetraacetate gave **12** in 52% over-all yield from **11**. Oxidation of **11**, **16**, and the "7–6" bicyclic enol ethers **27** and **28** with MCPBA gave the corresponding keto lactones in 57–72% yields (Table IV). Implicit in the success of the MCPBA oxidation method is the recognition of the fact that ten- or eleven-membered ring keto lactones which are so formed will react with excess per acid to give dilactones only very slowly.[16] Such Baeyer–Villiger oxidation was not a complicating factor in any of the ten- or eleven-membered keto lactones that we synthesized. Treatment of **16** with excess MCPBA for 20 hr, however, gave a mixture of the desired 7-ketoundecanolide (**17**, 22% by semicarbazone formation) and what was probably both possible dilactones derived from **17**. A reaction time of 20 min was found to be sufficient for the oxidation of **16** and led to **17** in 72% yield (15–25% over-all yield from **13**). The 7-ketoundecanolide system is found in the Methymycin group of macrolide antibiotics.

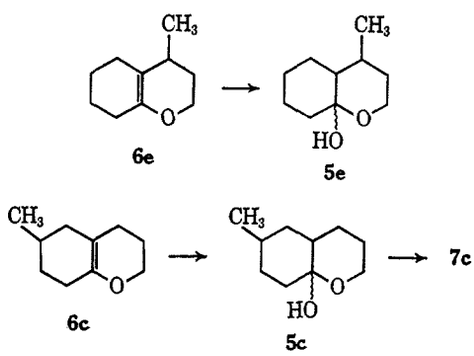
TABLE IV

OXIDATIONS OF BICYCLIC ENOL ETHERS TO KETO LACTONES

Enol ether	Keto lactone	Yield, % MCPBA	Yield, % Other
"6–7" **11**	6-Ketodecanolide (**12**)	71	52[a]
"7–7" **16**	7-Ketoundecanolide (**17**)	72	
"7–6" **27**	7-Ketodecanolide (**29**)	70.5	
4-Methyl "7–6" **28**	7-Keto-8-methyldecanolide (**30**)	57	

[a] Over-all yield from **11** *via* glycol formation (63%) and lead tetraacetate cleavage (82%).

Chromic Acid Oxidations of Tetrahydrochromans.—We have previously converted tetrahydrochromans directly into 6-ketononanolides with either MCPBA or ozone.[13] There have been two reports of the use of chromic acid in such oxidations. Schreiber[17] has oxidized the bicyclic enol ether group in N,N′-diacetylsolanocapsin to a lactam lactone in 42% yield with chromic acid while Carlson[18] has found that **6a** gave **7a** in *ca.* 60% yield with chromic acid. We have confirmed Carlson's results and find that chromic acid effectively oxidizes tetrahydrochromans to 6-ketononanolides (Table III). While the yields are reasonably comparable with those obtained *via* MCPBA oxidation, the ketononanolides obtained from the chromic acid oxidations are harder to purify and carry impurities through repeated distillation. The yields recorded in Table III were obtained with 1.00–1.44 ratios of chromium trioxide–tetrahydrochroman. When only 0.10 equiv of chromium trioxide was treated with 4-methyltetrahydrochroman (**6e**) the hydroxy ether **5e** was formed in 67% yield. A small yield (3%) of **5c** had been formed in the oxidation of 6-methyltetrahydrochroman (**6c**) with 1.00 equiv of chromium trioxide. When **5c** was further treated with 1.5 equiv of chromium trioxide, it was converted into the keto lactone **7c** (52% crude yield). Dehydration of **5c** with potassium pyrosulfate gave back **6c**. Furthermore **5c** so obtained was identical with the hydroxy ether obtained from the lithium aluminum hydride reduction of the enamine ester from 4-methylcyclohexanone (Table II).



Whereas further work is needed to clarify the pathways involved, these studies indicate that chromic acid oxidations are useful in keto-lactone synthesis.

The above syntheses illustrate the approaches presently being utilized in our laboratories in the synthesis of molecules approaching the complexity of Methymycin. Further studies on the chemistry and spectral characteristics of our keto-lactones will be presented elsewhere.

Experimental Section

Microanalyses were performed by Professor V. B. Fish of the Department of Chemistry, Lehigh University, and Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Beckman IR-8 infrared spectrophotometer. Nmr spectra were recorded on Varian A-60 and A-60-A spectrometers with tetramethylsilane (τ 10) as an internal standard. Melting points were taken on a "Mel-Temp" apparatus and are corrected while boiling points are uncorrected.

4-Bromobutyl Acetate (8) and 5-Bromopentyl Acetate (18).—To a mixture of tetrahydrofuran (54 g, 0.75 mol) and zinc chloride (0.020 g) at 0° was added acetyl bromide (61.5 g, 0.50 mol) with stirring. The reaction mixture was stirred at 0° for 30 min, allowed to warm to 25° over 1 hr, and then heated at reflux for 30 min. After being cooled, chloroform (300 ml) was added, and the mixture was washed with 100 ml of water, three 50-ml portions of sodium bicarbonate solution, and three 100-ml portions of water to yield 88.7 g (91%) of **8**, bp 92–93° (12 mm). The nmr spectrum (neat) exhibited a triplet centered at τ 5.97 (J = 6 Hz, 2 H of CH_2–O), a triplet centered at 6.52 (J = 6 Hz, 2 H of CH_2–Br), a singlet at 8.02 (3 H of acetyl), and a multiplet centered at 8.2 (4 methylene H); the ir spectrum (neat) showed a band at 1745 cm^{-1}. Previous syntheses of **8** involved excess acetyl bromide and gave products which gave high Br analyses.[8,9] *Anal.* Calcd for $C_6H_{11}O_2Br$: Br, 40.97. Found: Br, 41.36. In a similar manner tetrahydropyran (86 g, 1.0 mol) was treated with acetyl bromide (0.65 mol) at reflux for 2 hr to give **18**: 118 g (87%); bp 90–91.5° (2.5 mm) (lit.[8,9] bp 106–107° (12 mm)); ir spectrum (neat), 1735 (C=O) and 1370 cm^{-1} (C–CH_3); nmr very similar to that of **8**.

3-Bromopropyl Acetate (1).—To trimethylene glycol (76.0 g, 1.00 mol) maintained at 0° by an ice bath was added acetyl

(14) L. P. Kuhn, *J. Amer. Chem. Soc.*, **74**, 2492 (1952).

(15) For anomeric replacements in sugars see M. L. Wolfrom and A. Thompson in "The Carbohydrates," W. Pigman, Ed., Academic Press Inc., New York, N. Y., 1957, pp 194–202.

(16) J. L. Mateos and H. Menchaca, *J. Org. Chem.*, **29**, 2026 (1964).

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

(18) R. G. Carlson and R. G. Blecke, *J. Org. Chem.*, **32**, 3538 (1967).

bromide (246 g, 2.00 mol) dropwise with stirring over 4 hr. Stirring was continued for 15 min, and the reaction flask was then heated for *ca.* 1 hr until evolution of hydrogen bromide appeared to stop. Benzene (200 ml) was then added, and the resultant mixture was refluxed overnight with removal of *ca.* 100 ml of benzene (and *ca.* 5 ml of water) with a Dean–Stark trap. The residual solution was washed with four 50-ml portions of 10% potassium carbonate and with water, dried over magnesium sulfate, and distilled to give 145 g (0.802 mol, 80%) of **1**, bp 81–85° (20 mm) (lit.[19] bp 81–86° (20 mm)); slight impurity by vpc on a 20% SE-30 column. The nmr spectrum of **1** exhibited two triplets centered at τ 5.85 (CH_2–O) and 6.53 (CH_2–Br), a multiplet at 7.65–7.84 (2 H of C-2 methylene), and a singlet at 7.92 (3 H, of methyl).

Synthesis of Pyrrolidine Enamines of Substituted Cyclohexanones.—A mixture of the appropriate cyclohexanone and pyrrolidine (1.5–2.0 equiv) in benzene, in some cases with *p*-toluenesulfonic acid catalyst present (usually not needed for pyrrolidinocyclohexene formation), was boiled with azeotropic removal of water followed by distillation.[5] All of the pyrrolidinocyclohexenes were synthesized in this manner. Data on some of the enamines follow.

1-Pyrrolidino-4-*t*-butylcyclohexene (2b) was prepared in 91% yield from 4-*t*-butylcyclohexanone: bp 117–119° (0.35 mm); ir (CH_2Cl_2), 1710 (w, ketone), 1640 cm^{-1} (m).

1-Pyrrolidino-3,5-dimethylcyclohexene (2e) was prepared in 93% yield from a 22:3 *cis–trans* mixture of the isomers of 3,5-dimethylcyclohexanone (to be described more fully elsewhere), bp 146–147° (30 mm).

Reaction of Pyrrolidine Enamines with 1.—A mixture of 1-pyrrolidinocyclohexene (**2a**) (5.32 g, 0.0350 mol) and **1** (12.67 g, 0.700 mol) in toluene (50 ml) was heated at reflux for 15 hr; distilled water (10 ml) was added, and refluxing was continued for 30 min. The reaction mixture was cooled, 10% sulfuric acid (10 ml) was added, and the mixture was extracted with ether several times. The combined extracts were washed with water, dried, and distilled to give 1.40 g (0.0071 mol, 20%) of **2-(3′-acetoxypropyl)cyclohexanone (3a)**, bp 115–118° (0.7 mm). Similar reaction in acetonitrile gave **3a** in 33% yield. The ir spectrum (neat) of **3a** exhibited carbonyl peaks at 1715 (ketone) and 1735 (ester) cm^{-1}.

1-Pyrrolidino-4-*t*-butylcyclohexene (2b, 103.5 g, 0.50 mol) was alkylated with **1** (135.7 g, 0.75 mol) in boiling toluene for 24 hr with a similar work-up to give **4-*t*-butyl-2-(3′-acetoxypropyl)-cyclohexanone (3b)**, 39.4 g (31%), bp 150–158° (1.1 mm), as well as recovered **1** (51 g) and 4-*t*-butylcyclohexanone (45 g). The ir spectrum (neat) of **3b** exhibited bands at 1715 (ketone) and 1745 cm^{-1} (acetate C=O); the nmr spectrum (neat) showed a triplet centered at τ 6.02 (2 H of CH_2–O), singlets at 8.05 ($OCOCH_3$) and 9.05 (*t*-butyl 9 H), and multiplet centered at 7.75 and 8.4.

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.94; H, 10.41.

Hydrolysis of the Keto Esters to Form 9-Hydroxyhexahydrochromans or Tetrahydrochromans.—The keto acetate **3b** (25.4 g, 0.1 mol) was treated with 7% potassium hydroxide in ethanol (90 ml of reagent) at room temperature for 24 hr. Removal of solvent *in vacuo*, extraction of the residue with ether, drying of the ether solution, and removal of the ether gave a white crystalline solid, 19.3 g (91% of crude **5b**). Recrystallization from 1:1 ethanol–water or sublimation at a bath temperature of 75° (0.2 mm) gave **5b** with mp 86–86.5°. The ir spectrum (Nujol) of **5b** exhibited no carbonyl absorption, *i.e.*, no **4b** could be detected, and had hydroxyl absorption at 3390 and 3280 cm^{-1}.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.24; H, 11.38.

Similar treatment of **3a** gave **4a** and/or **5a** which was distilled with dehydration to give tetrahydrochroman **6a**, 64%, bp 67–73° (10 mm).

Reaction of Pyrrolidinocyclohexene 2a with 8.—Treatment of **2a** (15.1 g, 0.10 mol) with **8** (39 g, 0.20 mol) in toluene (100 ml) under reflux for 24 hr, followed by the addition of water (20 ml) heating for 30 min, separation of the organic layer, washing twice with 10% sulfuric acid (20 ml each) and thrice with water (20 ml each), and drying over magnesium sulfate, gave 18.5 g of **8**, bp 90–92° (11 mm), and 4.6 g (0.022 mol, 22%) of **2-(4′-acetoxybutyl)cyclohexanone (9)**, bp 134–135.4° (0.5 mm). Other runs gave **9** in 21, 40, and 42% yield. The ir spectrum (neat) exhibited peaks at 1740 and 1710 cm^{-1}; nmr spectrum (neat), showed a triplet centered at τ 6.02 (J = 6 Hz; 2 H of CH_2–O), a singlet at 8.07 (methyl of acetyl), and multiplets at 7.7–7.9, 8.2–8.8 (methylene H).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.12; H, 9.80.

2-(4′-Hydroxybutyl)cyclohexanone (10) and 2-Oxabicyclo-[5.4.0]undec-1(7)-ene (11).—A solution of **9** (25.2 g, 0.119 mol) in 7% ethanolic potassium hydroxide (7 g, 0.125 mol of KOH dissolved in 5 ml of water and diluted to 100 ml with ethanol) was kept at room temperature for 24 hr. After the solvents were removed *in vacuo*, the residue was dissolved in water (*ca.* 25 ml) and extracted with five 25-ml portions of ether to give crude **10**; the ir spectrum (neat) showed bands at 3420 (broad) and 1710 cm^{-1}. This was dissolved in dry benzene (100 ml), *p*-toluenesulfonic acid (0.1 g) was added, and water (1.1 ml, 0.06 mol) was azeotropically distilled out during 1.5 hr. The benzene solution was washed with sodium bicarbonate solution, dried, and distilled to give **11**, 13.9 g (74%), bp 91–92° (11 mm).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.92; H, 10.73.

Attempted distillation of **10** at 0.5 mm gave water and some **11**. The ir spectrum (neat) of **11** exhibited a band at 1685 cm^{-1} (enol ether). The nmr spectrum (neat) exhibited a triplet centered at τ 6.22 (2 H of CH_2–O), a multiplet centered at 8.05 (6 allylic H) and at 8.42 (8 methylene H).

Conversion of 11 into 6-Ketodecanolide. A. *Via* Glycol.—To **11** (7.6 g, 0.05 mol) in ether (50 ml) was added monoperphthalic acid in moist ether until after 8 hr there was an excess of per acid present. The resultant mixture was stirred for 12 hr (excess per acid still present), filtered, washed with saturated sodium bicarbonate solution, and dried over magnesium sulfate to yield, after removal of the ether *in vacuo*, crude 1,7-dihydroxy-2-oxabicyclo[5.4.0]undecane, 5.9 g (0.032 mol), or a maximum yield of 63%. To the crude glycol, 5.9 g (0.032 mol maximum), in dry benzene (150 ml) was added lead tetraacetate (22 g, 0.05 mol) with stirring. The resultant solution was allowed to stir at room temperature for 3 hr, glycerine was added, and the solution was gently warmed for 15 min. It was then filtered, washed with three 50-ml portions of a saturated sodium chloride solution, dried, and evaporated to give 5.4 g of crude product which was distilled to give 4.8 g (0.026 mol) of **12**, 82% from glycol or 52% over-all from **11**, bp 105° (0.6 mm).

B. *Via* MCPBA Oxidation.—Addition of **11** (15.2 g, 0.10 mol) in methylene chloride (50 ml) to MCPBA (85%, 60 g, 0.30 mol) in methylene chloride (350 ml) over 30 min (exothermic reaction) followed by room temperature reaction for 14 hr and work-up as previously described[4a] gave **12** (13.1 g, 0.071 mol, 71%), bp 105° (0.6 mm). The ir spectrum (neat) of **12** had carbonyl bands at 1735 (lactone) and 1715 cm^{-1} (ketone); the nmr spectrum ($CDCl_3$) showed multiplets centered at τ 5.98 (2 H of CH_2–O, *ca.* five peaks discernible), 7.58 (6 C-2, C-5, and C-7-H) and τ 8.22 (8 C-3, C-4, C-8, and C-9-H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.05; H, 8.99.

2-(4′-Acetoxybutyl)cycloheptanone (14).—Reaction of pyrrolidinocycloheptene (**13**) (82.5 g, 0.50 mol) with **8** (195 g, 1.00 mol) as described for **2a** above gave **14**, 54.4 g (48%)[10], bp 126–126.5° (0.3 mm), as a colorless liquid. The nmr spectrum ($CDCl_3$) exhibited a triplet centered at τ 5.95 (2 H of CH_2–O), a singlet at 7.98 (3 H methyl of acetyl), and other peaks for the remaining methylene protons; the ir spectrum (neat), showed bands at 1700 (ketone) and 1740 cm^{-1} (acetate).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.80; H, 9.74.

Hydrolysis and Dehydrative Cyclization of 14.—The hydrolysis of **14** (45.2 g, 0.20 mol) followed by azeotropic dehydration and cyclization for 8 hr as described above for **9** gave, after two distillations, 24.2 g (73%) of the enol ether **16**, bp 56–56.5° (0.3 mm), and a mixture of mainly 2-(4′-hydroxybutyl)cycloheptanone (**15**) with some **16** (7.7 g, 21% if pure **15**), bp 140–140.5° (0.75 mm). The ir spectrum (neat) of **16** exhibited a band at 1670 cm^{-1} (enol ether); the nmr spectrum ($CDCl_3$) showed a triplet centered at τ 6.15 (2 H of CH_2–O) and multiplets centered at 7.90 (allylic H) and 8.45 (other H). The ir spectrum of the mixture of **15** and **16** (neat) had bands at 3440 (moderate, broad, OH), 1710 (strong, C=O) and 1675 cm^{-1} (moderate, vinyl ether).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found for **16**: C, 79.31; H, 10.77.

(19) J. S. Allen and H. Hibbert, *J. Amer. Chem. Soc.*, **56**, 1398 (1934).

7-Ketoundecanolide (17).—A solution of **16** (4.15 g, 0.025 mol) in methylene chloride (15 ml) was added dropwise with stirring to MCPBA (85%, 15 g, 0.074 mol) in methylene chloride (90 ml) over 10 min causing the mixture to gently reflux. After being stirred for another 10 min, the reaction mixture was worked up as previously described to give **17**, 3.54 g (72%), bp 114–115° (0.3 mm), mp 42–43° (hexane). The infrared spectrum (CH_2Cl_2) of **17** exhibited carbonyl peaks at 1703 and 1725 cm^{-1}; nmr (CCl_4), a triplet at τ 5.90 (J = 5 Hz, 2 H of CH_2–O), and multiplets centered at 7.6 (6 H α to C=O) and 8.4 (other methylene H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.50; H, 8.96.

Reaction of **16** with a threefold excess of MCPBA for 20 hr gave a product, bp 117–120° (0.45 mm), whose nmr spectrum (CCl_4) indicated *ca.* 50% too much integrated area for the τ 5.90 peak (CH_2–O), *i.e.*, dilactone(s) and **17** were present. The mixture gave the semicarbazone of **17** (22% from **16**), mp 198–199°.

Anal. Calcd for $C_{12}H_{21}O_3N_3$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.53; H, 8.40; N, 16.32.

2-(5′-Acetoxypentyl)cyclohexanone (19).—Reaction of **2a** with 5-bromopentyl acetate **18** as described for the synthesis of **9** gave **19** (11–20%), bp 130–132° (0.075 mm). A sample was redistilled for analysis. The ir spectrum (neat) exhibited peaks at 1740 and 1710 cm^{-1}; nmr (CCl_4), a triplet centered at τ 6.03 (J = 6 Hz, 2 H of CH_2–O), a singlet at 8.01 (methyl), and multiplets at 7.7–7.9 and 8.1–8.8.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.87; H, 9.79.

2-(5′-Hydroxypentyl)cyclohexanone (20).—Hydrolysis of **19** with ethanolic potassium hydroxide as for **9** or **14** gave **20** in *ca.* 83% crude yield; the 2,4-dinitrophenylhydrazone had mp 120–121° (from ethanol; tlc showed one spot). The ir spectrum (neat) of **20** exhibited a broad peak at 3390 (H-bonded OH) and a carbonyl peak at 1710 cm^{-1}. The nmr spectrum (CCl_4) included a broad singlet at τ 5.8 (1 H of OH, exchangable with D_2O) and a multiplet centered at 6.5 (2 H of CH_2–O).

Anal. Calcd for $C_{17}H_{24}N_4O_5$: C, 56.10; H, 6.61; N, 15.37. Found: C, 55.89; H, 6.68; N, 15.21.

Attempts to Cyclize and Dehydrate 20 to the Enol Ether 21.—Treatment of **20** with *p*-toluenesulfonic acid in boiling benzene or toluene under azeotroping conditions (up to 17 hr) gave only starting material. Similar treatment in boiling xylene for 3 days gave a mixture of **20** and an olefin, probably **22**; the ir spectrum (neat) showed bands at 1710 (ketone) and 1600 cm^{-1} (olefin). Similar reaction in toluene followed by removal of the solvent and distillation *in vacuo* gave polymeric material; the ir spectrum (neat) showed bands at 1710 cm^{-1} and no hydroxyl or C=CH_2 absorption. Reaction of **20** (3.68 g, 0.020 mol) with trifluoroacetic anhydride (6 ml, 9.15 g) in benzene (300 ml) at room temperature (1 hr) and at reflux (17 hr), followed by washing with saturated sodium carbonate solution and water, and drying gave 2.85 g (0.0108 mol, 57%) of **19a** as a yellow oil: bp 167–170° (15 mm); one peak by vpc on 5% SE-30 on Chromosorb W; ir spectrum (neat), 1785 (trifluoroacetate), 1714 (cyclohexanone carbonyl), and 1353 cm^{-1} (CF_3; lit.[20] 1350–1120 cm^{-1} for CF_3); nmr spectrum (neat), a triplet centered at τ 6.03 (2 H of CH_2–O) and multiplets centered at 8.2 (3 H) and *ca.* 8.8 (14 H).

Pyrrolidinocycloheptene (13).—Reaction of cycloheptanone with pyrrolidine (1.5–2.0 equiv) and *p*-toluenesulfonic acid catalyst in toluene gave **13** in yields varying from 18 to 68% with average yields between 30 and 40%. The use of titanium tetrachloride[21] as catalyst (in benzene solution) gave poorer yields.

General Procedure for Reaction of Pyrrolidinocyclohexenes with an Acrylate Ester.—A mixture of pyrrolidinocyclohexene (**29**) (28.52 g, 0.189 mol) and ethyl acrylate (20.8 g, 0.208 mol) in absolute ethanol (100 ml) was heated at reflux for 18 hr and then distilled to give 43.32 g (0.172 mol, 91%) of **1-pyrrolidino-6-(2′-carbethoxyethyl)cyclohexene (31a)**, bp 108–115° (0.05 mm). The procedure is that of Stork and Etheredge.[11]

1-Pyrrolidino-4-*t*-butyl-6-(2′-carbethoxyethyl)cyclohexene (31b) was thus synthesized (94%): bp 180–207° (0.5 mm); ir (CH_2Cl_2), 1730 (s) and 1650 (w) cm^{-1}; nmr (CCl_4), quartet centered at τ 5.98 (CH_2 of ethyl), triplet centered at 8.82 (CH_3 of ethyl), singlet at 9.15 (*t*-butyl), and multiplets at *ca.* 6.9, 7.3, 7.8, and 8.3 (methylene H). A vinyl H was not evident.

1-Pyrrolidino-4-methyl-6-(2′-carbethoxyethyl)cyclohexene (31c) was prepared in 85% yield: bp 108–140° (0.025 mm); nmr (CCl_4), 0.81 H vinyl proton as a multiplet centered at τ 4.22.

1-Pyrrolidino-2-methyl-6-(2′-carbethoxyethyl)cyclohexene (31d) was prepared in 82% yield: bp 103–115° (0.07 mm); nmr (CCl_4), a quartet centered at τ 5.98 (CH_2 of ethyl), a triplet centered at 8.8 (CH_3 of ethyl), a singlet at 7.72 (vinyl methyl), a doublet centered at 9.1 (allylic methyl), and methylene multiplets.

1-Pyrrolidino-6-(1′-methyl-2′-carbomethoxyethyl)cyclohexene (31e) was prepared in 83% yield from **2a** and methyl crotonate: bp 135–142° (1.0 mm); nmr (neat), *ca.* 0.62 H vinyl proton as a multiplet centered at τ 4.65 (τ 4.64 in CCl_4); reaction in MeOH.

1-Pyrrolidino-6-(2′-methyl-2′-carbmethoxyethyl)cyclohexene (31f) was prepared in 89% yield from **2a** and methyl methacrylate: bp 250–265° (1.2 mm); nmr (CCl_4), 0.83–0.85 H vinyl proton as a multiplet centered at τ 4.24; reaction in MeOH.

1-Pyrrolidino-3,5-dimethyl-6-(2′-carbethoxyethyl)cyclohexene (31g), 67%, was prepared from the pyrrolidine enamine of 3,5-dimethylcyclohexanone (22:3 *cis/trans*) and ethyl acrylate: bp 168–169° (4.5 mm); nmr (CCl_4), *ca.* 0.65 H vinyl proton as a singlet at τ 4.40.

Michael Additions with Pyrrolidinocycloheptene. A. Reaction with Ethyl Acrylate.—A mixture of **13** (16.5 g, 0.10 mol) and ethyl acrylate (15.0 g, 0.15 mol) in absolute ethanol (200 ml) was heated at reflux for 15 hr with protection from moisture with a drying tube. After removal of solvent and other volatile species *in vacuo*, the residue was distilled to give the pyrrolidine enamine of 2-(2′-carbethoxyethyl)cycloheptanone (**23**) as a viscous yellow oil, 22.1 g (83.5%), bp 185–189° (0.35 mm). The ir spectrum (neat) of **23** exhibited peaks at 1730 (s, ester) and 1630 cm^{-1} (s, enamine); nmr (CCl_4), a multiplet centered at τ 5.60 (*ca.* 1 H, vinyl proton), a quartet centered at τ 5.95 (2 H, CH_2 of ethyl), a triplet centered at 8.75 (3 H, CH_3 of ethyl) and a complex multiplet at 7.0–8.55 including the CH_2–N protons centered at *ca.* 7.1. Similar reaction of **13** with methyl acrylate gave 2-(2′-carbomethoxyethyl)cycloheptanone (**23a**) (70%): bp 194–196° (1.5 mm); ir spectrum (neat), 1730 and 1640 cm^{-1}.

B. Reaction with Methyl Crotonate.—Similar reaction of **13** (12.0 g, 0.073 mol) with methyl crotonate (11.0 g, 0.11 mol) in ethanol gave the pyrrolidine enamine of 2-(1′-methyl-2′-carboalkoxyethyl)cyclohexanone (**24**) in *ca.* 72% yield: bp 125–134° (0.07 mm); ir spectrum (neat), 1625 and 1735 cm^{-1}; nmr (CCl_4), a multiplet centered at τ 5.6 (vinyl proton) and complex multiplets compatible with a mixture of methyl and ethyl esters.

Reduction of Enamine Esters with Lithium Aluminum Hydride.—The reduction of **31a** with lithium aluminum hydride in dry ether according to the general procedure of Stork and Etheredge[11] gave crude tetrahydrochroman **6a** (70%); bp 85–100° (20 mm), and 9-hydroxyhexahydrochroman **5a** (18%); ir spectrum of **5a** (neat), broad hydroxyl band centered at 3350 cm^{-1}, sharp ether band at 1060 cm^{-1}, and no carbonyl band.

6-Methyl-9-Hydroxyhexahydrochroman (5c), obtained in 52% yield, was synthesized similarly from **31c**, mp (after recrystallization from petroleum ether (bp 30–60°) and sublimation) 99–100°. The ir spectrum of **5c** (CCl_4) exhibited no carbonyl absorption, but showed OH at 3420 (broad, H bonded) and 3600 cm^{-1} (sharp, non H-bonded); the nmr spectrum (CCl_4) included a hydroxyl singlet at τ 7.15.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.77; H, 10.72.

Reduction of Enamine Esters and Subsequent Dehydration to Tetrahydrochromans. 8-Methyl-5,6,7,8-tetrahydrochroman (6d) was synthesized in 69% over-all yield, bp 95–112° (18 mm) (lit.[4a] bp 79–82° (12 mm)), *via* the above reduction procedure followed by distillation of the residue from potassium pyrosulfate (6 g for product from 0.265 mol of **31d**): nmr (CCl_4), multiplets centered at τ 6.10 (2 H of CH_2–O), 8.15 and 8.40 (methylene H), and a doublet centered at 8.95 (3 H of CH_3); ir (neat), 1685 cm^{-1}.

6-Methyl-5,6,7,8-tetrahydrochroman (6c) was similarly synthesized in 66% over-all yield from **31c** by distilling the crude residue from the hydride reduction from a trace of *p*-toluenesulfonic acid, bp 88–89° (10 mm). Alternatively the hydroxy ether **5c** (8.25 g, 0.0485 mol) was heated *in vacuo* with potassium pyrosulfate (0.83 g) to distil **6c** (5.07 g, 0.0334 mol, 69%):

(20) N. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., p 314.

(21) W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).

bp 98–108° (20 mm) (lit.[4a] bp 79–80° (12 mm)); nmr (CCl_4), multiplets centered at τ 6.06 (2 H of CH_2–O), 8.15 and a poorly resolved doublet centered at 9.05 (3 H of methyl); ir (neat), 1682 cm^{-1}.

4-Methyl-5,6,7,8-tetrahydrochroman (6e) was similarly synthesized in 78% yield, bp 82–83° (9 mm), *via* distillation of the hydride reduction product from *p*-toluenesulfonic acid. The nmr spectrum (neat) of **6e** exhibits a triplet centered at τ 4.20 (2 H of CH_2–O), multiplets centered at 8.10 and 8.40 (probably allylic plus C-3 protons and nonallylic protons, respectively), and a doublet centered at 9.03 (3 H of methyl); ir (neat), 1682 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.91; H, 10.59. Found: C, 78.99; H, 10.83.

3-Methyl-5,6,7,8-tetrahydrochroman (6f) was similarly synthesized and a 74% yield was obtained; bp 82–83° (9 mm). The nmr spectrum (neat) of **6f** exhibited a complex multiplet centered at τ 6.45 (CH_2–O), multiplets centered at 8.15 and 8.40 (other methylene protons), and a doublet centered at 9.03 (3 H of methyl).

Anal. Found: C, 78.92; H, 10.62.

5,7-Dimethyl-5,6,7,8-tetrahydrochroman (6g) was similarly synthesized and a 73% yield was obtained, bp 89° (9 mm). The nmr spectrum (neat) of **6g** exhibited complex multiplets centered at τ 6.18 (CH_2–O) and 8.22 (methylene H) and two unsymmetrical doublets centered at 9.05 and 9.12 (methyl H).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.61; H, 11.18.

6-*t*-Butyl-5,6,7,8-tetrahydrochroman was similarly synthesized in 69.5% yield from **5b** (see above) (63.5% over-all from acetoxy ketone **3b**): bp 75° (0.3 mm); ir spectrum (neat), 1695 (vinyl ether), 1370, 1385 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.14; H, 11.25.

Reduction of Enamine Esters to Hydroxypropylcycloheptanones. A. Synthesis of 25.—Similar reduction of **23** (20.55 g, 0.0755 mol) gave 16.44 g of **25** as an oil: ir spectrum (neat), broad OH band at 3350 (s) and carbonyl band at 1700 cm^{-1} (slightly stronger than OH); nmr (CCl_4), a singlet at τ 5.84 (1 H of OH, exchangable with D_2O), a multiplet at 6.50 (2 H of CH_2O), and multiplets at 7.2–7.4 and 8.5. The ir spectrum (CH_2Cl_2) exhibited peaks at 4000 (sharp, free OH), 3390 (broad H-bonded OH), and 1700 cm^{-1} (C=O).

B. Synthesis of 26.—Similar reduction of **24** gave crude **26** which was directly converted into the enol ether **28** (see below).

Synthesis of the "7–6" Enol Ethers 27 and 28. A. Enol Ether 27.—Distilled **25** (9.32 g) was treated with *p*-toluenesulfonic acid, slowly warmed to boiling at reduced pressure, and distilled several times to give **27** (1.46 g, 12.5%), bp 78–124° (4.0 mm), and recovered **25** (8.69 g). The ir spectrum (neat) of **27** exhibited absorption at 1680 cm^{-1}; the nmr (CCl_4) spectrum showed multiplets centered at τ 6.23 and 6.45 (CH_2–O), 8.12, and 8.40. In another run crude **25** was directly treated as above to give 32% of **27**.

B. Enol Ether 28.—Crude **26** was dissolved in benzene (200 ml), a few crystals of *p*-toluenesulfonic acid were added, and water was azeotropically removed as above to give 5.8 g (67% over-all from **24**) of **28** as a colorless liquid: bp 79–81° (2.0 mm); ir spectrum of **28** (neat), 1670 cm^{-1}; nmr (neat), multiplet centered at τ 6.25 (2 H of CH_2–O), multiplets centered at 7.25 (1 H methine proton), 8.0 (4 allylic H and 2 H of C-3 methylene β to oxygen), and at 8.43 (other methylene H), and a doublet centered at 9.05 (J = 7 Hz, 3 H of methyl).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.61; H, 11.13.

7-Ketodecanolide (29).—Addition of **27** (1.30 g, 0.00855 mol) in methylene chloride (10 ml) dropwise to a stirred suspension of MCPBA (4.4 g, 3 equiv) in methylene chloride (20 ml) followed by stirring at room temperature and work-up as before gave **29**, 1.11 g (70.5%), as a colorless liquid: bp 82–86° (0.15 mm); vpc, one peak (5% SE-30); ir spectrum (neat), 1730 and 1710 cm^{-1}; nmr (CCl_4), a triplet centered at τ 5.94 (2 H of CH_2–O) and multiplets centered at 7.6, 7.85, and 8.52.

The 2,4-dinitrophenylhydrazone of **29**, a yellow solid, had mp 178–179° dec (from EtOAc–petroleum ether).

Anal. Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.53; H, 5.62; N, 15.26.

7-Keto-8-methyldecanolide (30).—Similar oxidation of **28** with MCPBA gave **30**: 57%; bp 98–106° (0.065 mm); vpc, 98% one peak with a 2% forepeak (on 20% SE-30); ir spectrum (neat), 1733 and 1714 cm^{-1}; nmr (CCl_4), multiplets centered at τ 5.95 (five lines, 2 H of CH_2–O), 7.32, 7.8, 8.6, and a doublet centered at 8.94 (J_{HH} = 7 Hz, 3 H of methyl).

The 2,4-dinitrophenylhydrazone of **30**, a yellow powder, had mp 146–147° (from EtOAc–petroleum ether).

Anal. Calcd for $C_{17}H_{22}N_4O_6$: C, 54.10; H, 5.61; N, 14.85. Found: C, 54.14; H, 5.79; N, 14.95.

Ketolactone Formation by MCPBA Oxidation of Tetrahydrochromans.—The previously described procedure[4a] involving the addition of tetrahydrochroman to a threefold excess of MCPBA was used as follows.

7-Methyl-6-ketononanolide (7e) was synthesized in 56% yield: bp 93–94° (0.15 mm); ir spectrum (neat), 1740 and 1712 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.99; H, 8.98.

8-Methyl-6-ketononanolide (7f) was obtained in 50% yield: bp 104–106° (0.2 mm); mp 60–60.5°; ir spectrum (neat), 1740 and 1712 cm^{-1}.

Anal. Found: C, 65.25; H, 8.63.

2-Methyl-6-ketononanolide (7d) was obtained in 64% yield: bp 100–103° (0.7 mm); ir spectrum (neat), 1715 (ketone) and 1733 cm^{-1} (lactone); identical ir and nmr spectra with that of **7d** as previously reported.[4a] The addition of MCPBA (3 equiv) to **6d** gave a decreased yield of **7d** (37%).

4-*t*-Butyl-6-ketononanolide (7b, 76%) had bp 114–114.5° (0.4 mm); ir spectrum (neat), 1715 and 1735 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.10; H, 9.72.

3,5-Dimethyl-6-ketononanolide (7g, 51%) had bp 88–89° (0.25 mm). The nmr spectrum (CCl_4) exhibited a triplet centered at τ 5.85 (CH_2–O), complex multiplets centered at *ca.* 7.85 (methylene H), and two poorly resolved doublets at 8.92–9.08 (methyl H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.75; H, 9.29.

Cleavage of Glycol 33 with MCPBA to Give Keto Lactone 7a.—A mixture of **33** (1.31 g, 0.00765 mol) and MCPBA (85% pure, 2.46 g, *ca.* 0.014 mol) in methylene chloride (25 ml) was stirred at room temperature for 15 hr. No visible change was seen, and magnesium sulfate was added to remove any water which may have formed. The mixture was again stirred for 15 hr, then washed with 5% potassium carbonate containing sodium bicarbonate and then with water, dried, and evaporated to give crystalline **7a** (0.944 g, 0.00555 mol, 70%) with the proper ir spectrum.

Solubility of MCPBA and MCBA in Methylene Chloride.—Saturated solutions of *m*-chloroperbenzoic acid (MCPBA) and of *m*-chlorobenzoic acid (MCBA) were prepared at *ca.* 24°. Samples (1 ml) were removed volumetrically and evaporated to dryness in tared flasks. The saturated solution of MCPBA contained 156 mg/ml, while the solution of MCBA contained 30 mg/ml.

Infrared Studies on Glycol 34.—A saturated solution of **34** in CH_2Cl_2 gave sharp hydroxyl absorption at 3580 cm^{-1} while a 0.5 *M* solution in CCl_4 gave a sharp OH (free OH) at 3610 and a broad OH (H-bonded) at 3410 cm^{-1}. The CH_2Cl_2 solution was apparently more dilute than 0.5 *M*.

Chromic Acid Oxidations of Tetrahydrochromans to Keto Lactones.—In a typical procedure, to a well-stirred and cooled (ice–salt bath) solution of 3-methyltetrahydrochroman **6f** (15.2 g, 0.10 mol) in acetone (250 ml) was added dropwise (at 0°) a mixture of chromium trioxide (13.32 g, 0.133 mol), concentrated sulfuric acid (10.6 ml), and water (36 ml). After completion of the addition, the mixture was warmed to room temperature, stirred for 1 hr, excess chromic acid was reduced with solid sodium bisulfite, and the acetone solution was decanted. The remaining sludge was washed several times with ether, the washings were combined with the acetone solution, and the resultant solution was evaporated and distilled to give 13.1 g (71%) of **7f**, mp 58–61°. These oxidations gave 6-ketononanolides with a persistent yellow impurity which was not removed upon repeated distillation.

Chromic Acid Reactions Which Give 9-Hydroxyhexahydrochromans.—The above procedure on 6-methyltetrahydrochroman (**6c**) gave, in addition to a 47% yield of 4-methyl-6-ketononanolide (**7c**), a 3% yield of 6-methyl-9-hydroxyhexahydrochroman (**5c**), mp 80–83°, mmp 93–96°, with genuine **5c** of mp 95–96° (from enamine ester reduction as above). Treatment of 4-methyltetrahydrochroman (**6e**) (15.2 g, 0.10 mol) with 0.1 equiv of chromic oxide as above gave 11.4 g (0.067 mol,

67%) of 4-methyl-9-hydroxyhexahydrochroman (**5e**), mp 89–90°. The nmr spectrum ($CHCl_3$) included a hydroxyl singlet at τ 6.97; the ir spectrum (0.5 *M* CCl_4) showed bands at 3610 (sharp, free OH) and 3410 cm^{-1} (broad, H-bonded OH).

Anal. Found: C, 70.54; H, 10.80.

Chromic Acid Oxidation of 5c.—Treatment of **5c** (3.69 g, 0.0217 mol) with the above general chromic acid procedure using 0.0319 mol of chromium trioxide gave 4-methyl-6-ketononanolide (**7c**) in 52% yield, bp 105–111° (1.5 mm), with spectra (ir and nmr) identical with those of genuine **7c**.

Dehydration of 5c with Potassium Pyrosulfate.—A mixture of **5c** (8.25 g, 0.0485 mol) and potassium pyrosulfate (0.83 g) was distilled *in vacuo* to give 7.22 g of crude, wet material which was dried in ether solution. After solvent evaporation the residue was distilled to give 6-methyltetrahydrochroman (**5c**): 5.07 g (69%); bp 98–108° (20 mm); identical spectral characteristics (ir and nmr) with those of genuine **6c**.

Registry No.—**2b**, 4147-00-6; **3b**, 16120-95-9; **5b**, 16120-96-0; **5c**, 16120-97-1; **5e**, 16199-04-5; **6b**, 13030-87-0; **6c**, 13030-81-4; **6d**, 13030-80-3; **6e**, 16121-01-0; **6f**, 16121-02-1; **6g**, 13030-86-9; **7b**, 16121-04-3; **7e**, 16121-05-4; **7f**, 16121-06-5; **7g**, 16121-07-6; **8**, 4753-59-7; **9**, 4753-60-0; **11**, 4802-49-7; **12**, 4753-58-6; **14**, 16121-10-1; **16**, 16121-13-4; **17**, 16121-14-5; semicarbazone of **17**, 16121-33-8; **19**, 16121-27-0; 2,4-dinitrophenylhydrazone of **20**, 16121-28-1; **23**-(7-ene), 16121-15-6; **23** (1-ene), 16121-26-9; **25**, 16121-16-7; **27**, 16121-17-8; **28**, 16121-18-9; **29**, 16121-19-0; 2,4-dinitrophenylhydrazone of **29**, 16121-34-9; **30**, 16121-20-3; 2,4-dinitrophenylhydrazone of **30**, 16121-35-0; **31b** (6-ene), 16121-29-2; **31b** (1-ene), 16121-30-5; **31** (6-ene), 16121-31-6; **31c** (1-ene), 16121-32-7; **31d** (6-ene), 16121-21-4; **31d** (1-ene), 16121-22-5; **31e** (6-ene), 16121-23-6; **31e** (1-ene), 16121-36-1; **31f** (6-ene), 16121-24-7; **31f** (1-ene), 16121-37-2; **31g** (6-ene), 16121-25-8; **31g** (1-ene), 16121-38-3.

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meso-Dihydroanthracene Chemistry. II. The Preparation of 1,5- and 1,8-Dimethylanthraquinones[1]

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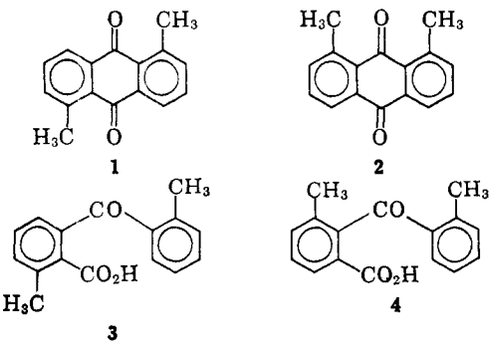
Syntheses of 1,5- (**1**) and 1,8-dimethylanthraquinone (**2**) *via* sulfuric acid catalyzed ring closures of 6-methyl-2-(2-methylbenzoyl)benzoic acid (**3**) and 3-methyl-2-(2-methylbenzoyl)benzoic acid (**4**), *via* ring closures of the corresponding benzylbenzoic acids **18** and **19** and *via* Diels–Alder reactions between 1,3-pentadiene and *p*-benzoquinone, have been studied. Of these, the diene synthesis, followed by oxidation, is probably the most convenient. Ring closures of the benzylbenzoic acids to 1,5-dimethylanthrone (**20**) and 4,5-dimethylanthrone (**21**) proceeded without rearrangement and in good yield, while those of the benzoylbenzoic acids **3** and **4** proceeded with attendant Hayashi rearrangement to give identical mixtures of **1** and **2** from both acids. The effect of sulfuric acid concentration upon the ratio of **1** to **2** was negligible, while the ratio of 6-methyl acid **3** to 3-methyl acid **4** obtained upon dilution of the acid solutions was markedly dependent upon sulfuric acid concentration. The Hayashi rearrangement of 3-methylbenzoylbenzoic acids to 6-methyl acids was shown (for the first time) to be a reversible process. These facts are rationalized with the Newman–Sandin mechanisms for the Hayashi rearrangement and for anthraquinone formation.

Our interest in the stereochemistry of 1,4-conjugate elimination[1,2] from 9,10-dihydro-9,10-anthradiol derivatives led us to a utilization of anthraquinones as reaction intermediates. These can be readily reduced to the desired diols.[1,3] The preparation of anthraquinones by acid-catalyzed cyclization of *o*-benzoylbenzoic acids[4] seemed to offer a ready procedure for the synthesis of 1,5-dimethylanthraquinone (**1**) and the 1,8-analog (**2**) in view of the availability[5] of the two isomeric benzoylbenzoic acids **3** and **4** from the reaction of *o*-tolylmagnesium bromide and 3-methylphthalic anhydride.



The sulfuric acid catalyzed cyclization of *either* **3** or **4** led to mixtures containing approximately 80% of the 1,5-dimethylquinone (**1**) and 20% of the 1,8-dimethylquinone (**2**). Both **1** and **2** were stable to the reaction conditions. Quinone **1** has been described previously[6] and was reduced by zinc in ammonia to 1,5-dimethylanthracene, also of known structure.[6] Neither quinone **2** nor 1,8-dimethylanthracene has been reported, but we now have (see below) prepared them by unequivocal syntheses.

The formation of both **1** and **2** from either **3** or **4** is

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