Hemiacetal Mediated Reactions. Directed Synthesis of Diols and Acetals

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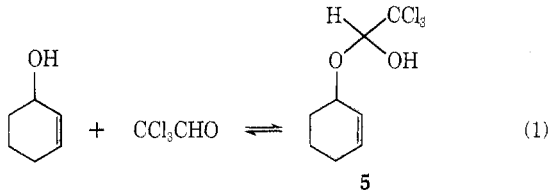
The mercuric trifluoroacetate promoted intramolecular addition of trichloroacetaldehyde (chloral) hemiacetal derivatives of unsaturated alcohols to carbon–carbon double bonds is reported. This process results in the intramolecular delivery of an oxygen nucleophile by the hydroxyl group. The chloral acetal products are converted to the corresponding diols by reduction. In several cases this overall process results in a highly specific conversion of a cyclic or acyclic unsaturated alcohol into a single diol product. For example, the equatorial allylic cyclohexenols **1a**, **1b**, and **10** are transformed in overall yields of 60–80%, and >99% isomeric purity, into the corresponding *cis*-1,2-diols **3a**, **3b**, and **12**, respectively. The scope and limitations of this process for the directed hydration of cyclic and acyclic unsaturated alcohols is described.

The importance of the alcohol function as a handle for directing the stereospecific establishment of new asymmetric centers and for controlling regiochemistry in stereorational organic synthesis is well recognized.[1] The secondary alcohol group is particularly useful in this sense since its stereospecific introduction by reduction is one of the best studied of all organic synthetic reactions.[2] We began a few years ago studies aimed at using the alcohol functionality as a handle to direct the addition of "complexed" nucleophiles to neighboring electrophilic centers.[3] We wish at this time to report our studies of the addition of hemiacetal derivatives of unsaturated alcohols to neighboring carbon–carbon double bonds, a process which results in the intramolecular delivery of an oxygen nucleophile (a "water equivalent") by the hydroxyl group. In several cases this process results in a highly specific conversion of a cyclic or acyclic unsaturated alcohol into a single diol product.

Results

Owing to its high propensity for forming hemiacetals,[4] trichloroacetaldehyde (chloral) was chosen for our preliminary work. The addition of 2 equiv of chloral to a solution of a primary or secondary alcohol in an aprotic solvent such as tetrahydrofuran (THF) resulted in quantitative formation of the hemiacetal derivative, *e.g.*, eq 1. Hemiacetal formation was easily monitored by observing the appearance of the characteristic singlet, in the nmr spectrum, near τ 5 for the methine hydrogen attached to the trichloromethyl-bearing carbon (see Table I).[5] To promote addition of the hemiacetal hydroxyl group to the neighboring double bond, mercuric trifluoroacetate was chosen, since it is both soluble in the aprotic solvents necessary for hemiacetal formation and is known to promote the addition of a variety of nucleophiles to carbon–carbon double bonds.[6,7] Treatment at room temperature of a THF solution of 2-cyclohexen-1-ol (**1a**, 0.5 *M*) and chloral (1.0 *M*) with mercuric trifluoroacetate (0.5 *M*) for 48 hr followed by demercuration[8] with alkaline sodium borohydride afforded the known[9] cyclic chloral adduct **3a** in 62% distilled yield (see Scheme I). The observation of two singlets (total of one hydrogen) in the nmr spectrum at τ 4.59 and 4.76 indicated that **3a** was a 92:8 mixture of epimers at the trichloromethyl-bearing carbon. The alternate possibility, that a mixture of cis–trans or positional isomers was formed, was ruled out by removal of the $CCl_3CH<$ group.



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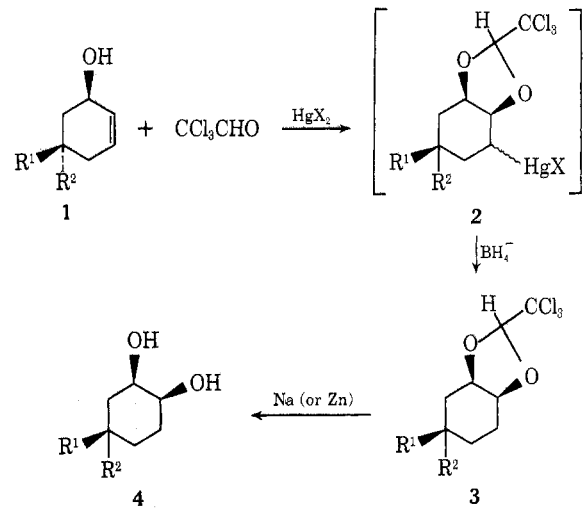
Scheme I



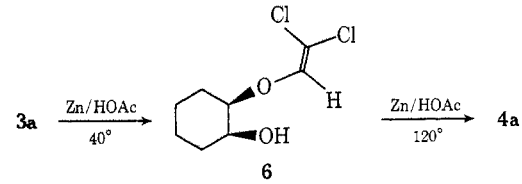
X = $OCOCF_3$

a, $R^1 = R^2 = H$

b, $R^1 = t$-Bu; $R^2 = H$

c, $R^1 = H$; $R^2 = t$-Bu

Although acetal **3a** was extremely resistant to cleavage by acids,[10] it could be cleaved in nearly quantitative yield by either of two reductive methods: (a) treatment for 24 hr with excess zinc dust in refluxing acetic acid (the diacetate is isolated)[11] or (b) treatment for 12 hr with excess sodium dispersion in ether.[12] The two reductive steps have quite different rates, since treatment of **3a** with zinc for 2 hr at 40° afforded cleanly vinyl ether **6** characterized



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by OH stretching absorption in the ir at 3400 cm^{-1} and a one-hydrogen singlet for the olefinic hydrogen at τ 3.33 in the nmr. The diol (or diacetate) formed by either reductive method was shown to be the *cis*-1,2-diol **4a**, uncontaminated (gc) by other isomers.

The time course of cyclic acetal formation was studied in detail for **1a**. Build-up of **2a** (characterized after demercuration to **3a**) occurred slowly and reached a maximum only after 50 hr (see Figure 1). On the other hand, hemiacetal **5** disappeared rapidly and was present to the extent of only 22% 15 min after the addition of mercuric trifluo-

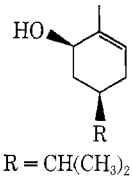
Table I
^{1}H Nmr Chemical Shifts of Hemiacetals

Hemiacetal	Solvent	τ CHCCl$_3$[a]	τ CH$_2$OCHCCl$_3$[b] OH
15	CCl_4	5.14	5.77
22	C_6H_6	5.23	6.25
23	C_6H_6	5.27	6.42
5	CCl_4	5.11	5.97
1-Hexanol[c]	C_6H_6	5.34	6.33
1-Hexanol[d]	CCl_4	4.53	6.47

[a] Singlet. [b] Center of multiplet. [c] Chloral hemiacetal. [d] Benzaldehyde hemiacetal.

roacetate. Change of the solvent to a mixture of THF and cyclohexane (1:1)[13] or the use of mercuric acetate in dimethylformamide did not improve the rate or yield of **3a** formation.

Our studies of the scope of the chloral cyclization reaction are summarized in Table II. For cyclic alcohols adduct formation occurs readily with equatorial allylic alcohols **1a**, **1b**, and **10**, and fails completely for the axial allylic alcohol **1c**, the homoallylic alcohol 3-cyclohexen-1-ol, and 2-cycloocten-1-ol. A serious limitation is that the double bond cannot be trisubstituted, since a competing oxidation reaction predominates.[7] For example, treatment of the cyclic enols (−)-carvotanacetol (**13**), (−)-carveol (**14**),



13, R = $CH(CH_3)_2$
14, R = $C(CH_3)=CH_2$

or cholest-4-en-3β-ol with chloral and mercuric trifluoroacetate resulted within 4–8 hr in the formation of a gray precipitate [presumed to be $Hg_2(OCOCF_3)_2$].[8c] The occurrence of an oxidation reaction is well documented in solvomercuration of tri- and tetrasubstituted olefins.[7,8c,15,16] As with **3a** the structure of the chloral adducts **3b**, **8**, and **11** was confirmed by reductive cleavage to afford the corresponding 1,2-diols (Table II).

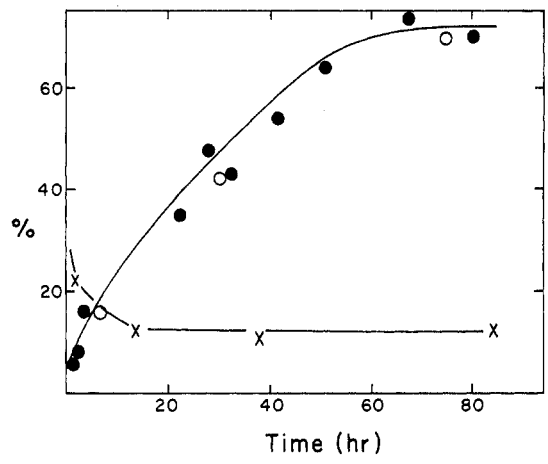
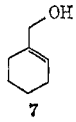
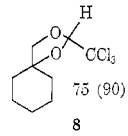
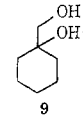
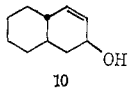
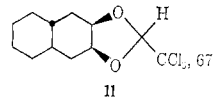
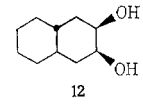


Figure 1. Rate of formation of cyclic acetal **3a** in THF (●) and in 1:1 THF–cyclohexane (○) as determined by gc, and the rate of disappearance of hemiacetal **5** in THF (X) as determined by the disappearance of the olefinic hydrogens in the nmr. Initial conditions were [**5**] = $Hg(OCOCF_3)_2$ = 0.5 *M*.

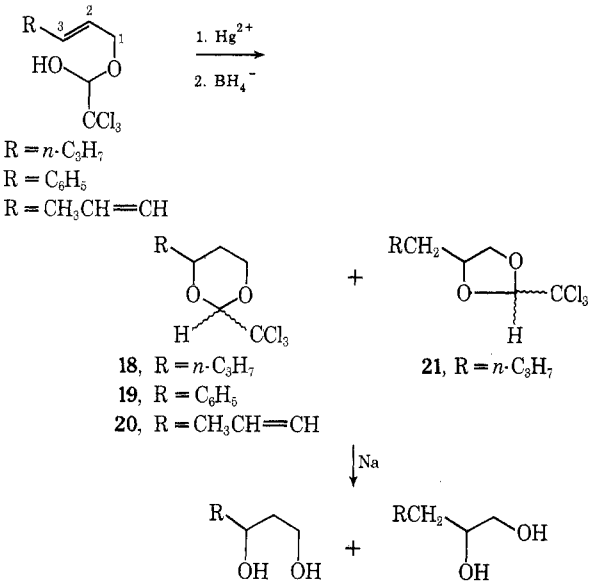
Formally cyclization of the hemiacetal derivatives of unsaturated acyclic alcohols can occur to afford products of two ring sizes. Mercuric trifluoroacetate treatment of the hemiacetal derivative of (*E*)-2-hexen-1-ol (**15**) in THF followed by demercuration affords a mixture of cyclic acetals **18** and **21** (Scheme II). The nmr spectrum of this mixture shows three singlets at τ 5.29, 4.79, and 4.72 (total of one hydrogen) for the >CHCCl$_3$ methine hydro-

Table II
Chloral Mediated Conversion of Unsaturated Alcohols into Cyclic Trichloroacetals and Diols

Unsaturated alcohol	Mercuration[a] Time, hr	Mercuration[a] Solvent	Cyclic trichloroacetal, % yield[b]	Diol products[c,d]
1a	60	THF	**3a**, 62 (80)	**4a**
1b	48	THF	**3b**, 74 (94)	**4b**
 7	28	THF	 75 (90) 8	 9
 10	66	THF	 11	 12
(*E*)-2-Hexen-1-ol	23	THF	**18** and **21**, 79 (94)	1,3-Hexanediol (56%), 1,2-hexanediol (44%)
	24	Benzene	**18**, 72	1,3-Hexanediol (83%), 1,2-hexanediol (17%)
(*E*)-Cinnamyl alcohol	60	THF	**19**, 63	$C_6H_5CHCH_2CH_2OH$ | OH
(*E*)-3-Hexen-1-ol	60	THF	**25** and **27**, 32 (44)[e]	1,3-Hexanediol (45%), 1,4-hexanediol (55%)
		Benzene	**25** and **27**, 32[e]	1,3-Hexanediol (92%), 1,4-hexanediol (8%)
(*Z*)-3-Hexen-1-ol	48	THF	**25** and **27**, 72 (92)	1,3-Hexanediol (65%), 1,4-hexanediol (35%)
		Benzene	**25** and **27**, 75	1,3-Hexanediol (91%), 1,4-hexanediol (9%)
(*E*)-3-Hepten-1-ol	48	THF	**26** and **28**, 55 (68)[f]	1,3-Heptanediol (40%), 1,4-heptanediol (60%)
2,4-Hexadien-1-ol[g]	36	THF	**20**, 43	1,2-Hexanediol (13%), 1,3-hexanediol (87%)[h]

[a] In THF at 25°, [enol], $Hg(OCOCF_3)_2$ = 0.5 *M*, [CCl_3CHO] = 1.0 *M*. [b] Distilled yield. Yields in parentheses were determined by gc analysis using internal standards. [c] For reactions in THF this is the kinetic product ratio while in benzene equilibration occurs (see Experimental Section). [d] Prepared in >85% yield by reduction method b and analyzed as the diacetates by gc. [e] 50% unreacted alcohol by nmr analysis. [f] 32% unreacted alcohol by nmr analysis. [g] A mixture of isomers. [h] Analyzed after hydrogenation.

Scheme II



15, R = n-C_3H_7
16, R = C_6H_5
17, R = $CH_3CH{=}CH$

18, R = n-C_3H_7
19, R = C_6H_5
20, R = $CH_3CH{=}CH$

21, R = n-C_3H_7

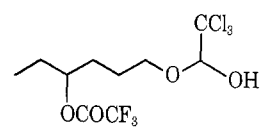
gens of three of the four possible isomers of **18** and **21**. The composition of this isomer mixture remains constant up to 24 hr, but changes thereafter. As a result the kinetic product ratios for this and other cyclic acetal mixtures were determined at short reaction times (see Experimental Section). Confirmation of the gross structure of this isomer mixture was achieved by reductive removal of the $CCl_3CH<$ group to afford a 44:56 mixture of 1,2-hexanediol and 1,3-hexanediol, implying a similar ratio for the 1,3-dioxolane isomer **21** and the 1,3-dioxane isomer **18** respectively. Equilibration to afford the more stable cyclic adduct is apparently more rapid in benzene, as acetal **18** is the predominant product formed after 24 hr in this solvent. Related work in the literature on mercurative cyclization of unsaturated alcohols (4-en-1-ols) indicates a kinetic preference for cyclization to afford the five-membered ring (tetrahydrofuran) rather than the six-membered (tetrahydropyran) product.[17]

Mercuration–demercuration of the homoallylic alcohol hemiacetals **22–24** also affords a mixture of cyclic acetals (Scheme III). Again the gross structure was confirmed by reduction to afford a mixture of 1,3- and 1,4-diols (Scheme III and Table I). Surprising is the large amount of the seven-membered ring 1,3-dioxepane isomer (**27** or **28**) which is formed in the kinetic product mixture. In fact, for the trans isomers **22** and **24** there is an apparent kinetic preference for formation of the dioxepane isomers. This kinetic preference for formation of the seven-membered ring adducts is unprecedented. For example, the E and Z isomers of octadec-5-en-1-ol (**29**) are reported to afford only the tetrahydropyran derivative **30** upon treatment in dimethylformamide with mercuric acetate.[17] A small amount (1–4%) of a seven-membered ring product, 2,7-dimethyloxepane, has, however, been reported by Brown from mercuration–demercuration of 1,7-octadiene with mercuric acetate in THF–H_2O.[6c]

29 **30** (100%)

R = $C_{12}H_{25}$

Several control experiments were performed to confirm that the seven-membered ring acetals were formed during mercuration and not during the alkaline demercuration step. (1) Treatment of 1,4-hexanediol for 24 hr with chloral (2 equiv) and mercuric trifluoroacetate (1 equiv) followed by alkaline borohydride treatment afforded no cyclic acetal and resulted in near-quantitative recovery of the diol. (2) Similar treatment of a 1:1 mixture of (*E*)-3-hexen-1-ol and 1,4-hexanediol resulted in formation of no more **27** than is formed in the absence of the diol. (3) Treatment of 1,4-hexanediol sequentially with chloral (1 equiv) and trifluoroacetic anhydride (1 equiv), to prepare *in situ* **31** (40% by nmr), followed by alkaline borohydride



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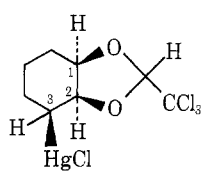
treatment, afforded no cyclic acetal **27**. As in the allylic case, change of the solvent to benzene resulted in a cleaner product mixture, and both **22** and **23** afforded after 24 hr an acetal mixture rich in the 1,3-dioxane isomer.

The stereochemical relationship between the trifluoroacetoxymercuri group and the chloral-derived oxygen atom is of interest. Most often a trans relationship, resulting from the usual anti addition mechanism, is observed between HgX and X of the kinetically formed olefin-HgX_2 adduct;[7,18] however, examples of the kinetic formation of cis adducts are known.[19] Several examples also exist in the cyclohexane series of thermodynamically controlled isomerization of the initially formed trans-diaxial adduct.[20] The nmr spectrum of the chloromercuri adduct **32** allows the assignment of a cis relationship between the



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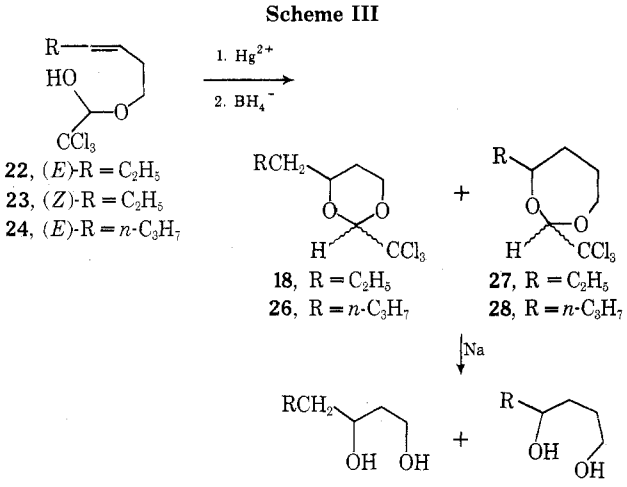
HgCl group and the oxygen atom at C-2. The chloromercuri adduct was isolated (crude yield 46%) by quenching the mercuration of **1a** with sodium chloride, rather than sodium borohydride, and was purified by recrystallization from benzene. The hydrogen bonded to the chloromercuri-bearing carbon appeared as a multiplet centered at τ 7.23 with a half-height bandwidth of 19 Hz. This hydrogen is therefore clearly axial[21] and thus the two possible chair cyclohexane structures (ignoring for the moment the $>CHCCl_3$ group) are **33** and **34** (Scheme IV). Although H_1 and H_2 appear as overlapping multiplets in deuteriochloroform, they are clearly resolved in pyridine.[19d,22] In pyridine H_2 appears as the four-line X portion of an AMX system centered at τ 4.92 and H_1 as a complex multiplet

Scheme III

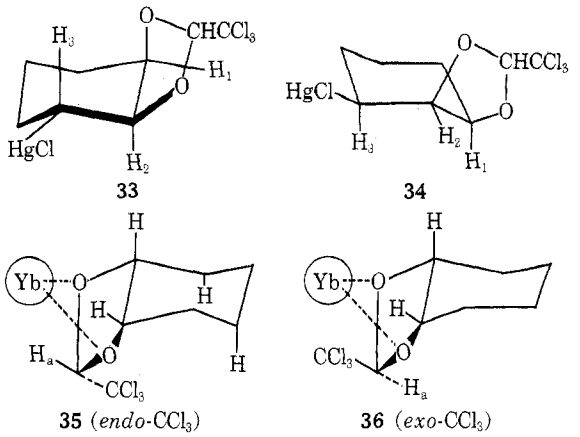


22, (*E*)-R = C_2H_5
23, (*Z*)-R = C_2H_5
24, (*E*)-R = n-C_3H_7

18, R = C_2H_5
26, R = n-C_3H_7

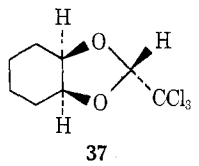
27, R = C_2H_5
28, R = n-C_3H_7

Scheme IV



centered at τ 5.38. The observed coupling constants for H_2 ($J_{1,2}$ and $J_{2,3}$) of 4.6 and 5.8 Hz are most consistent with the two axial–equatorial coupling expected for the cis isomer **34**, and, except for the possibility that there are major distortions caused by the fused five-membered ring, are inconsistent with structure **33** and its expected axial–axial coupling.[21]

Stereochemical assignments for the $>CHCCl_3$ group of the **3a** and **3b** epimer mixture were tentatively made by assuming that the major isomer would have the bulky CCl_3 group oriented exo, isomer **37**. This assignment has



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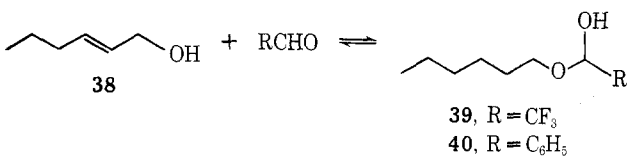
been confirmed by lanthanide-induced nmr shift experiments. If one makes the reasonable assumption that the shift reagent will complex with the acetal oxygens only from the less hindered exo side[23] (see **35** and **36** of Scheme IV), then one predicts that a major effect expected upon adding the lanthanide is a pronounced shift for the methine hydrogen H_a of isomer **35** and a correspondingly small shift for isomer **36**. Such behavior was observed when the **3a** epimer mixture was treated with $Yb(dpm)_3$; H_a of the minor isomer experienced a downfield shift of 4 ppm mol^{-1} mol^{-1}, while the corresponding shift for the major isomer was only 0.1 ppm mol^{-1} mol^{-1} (see Figure 2).

Changes in the aldehyde portion of the hemiacetal intermediate were briefly studied. The trifluoroacetaldehyde (fluoral) hemiacetal of (*E*)-2-hexen-1-ol (**38**) could be pre-



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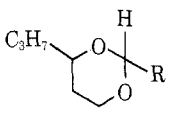
39, R = CF_3
40, R = C_6H_5



41, R = CF_3
42, R = C_6H_5

pared *in situ* by adding 1 equiv of **38** to a 1 *M* solution of fluoral (2 equiv) in diethyl ether at −78°. Ether solutions of hemiacetal **39** were stable at 25° for at least 24 hr, although excess fluoral rapidly degassed from solution at this temperature. Mercuration with mercuric trifluoroacetate for 90 hr followed by demercuration afforded in 52% yield the 1,3-dioxane fluoral adduct **41**, contaminated with 4% of the isomeric 1,3-dioxolane adduct.[24] As with

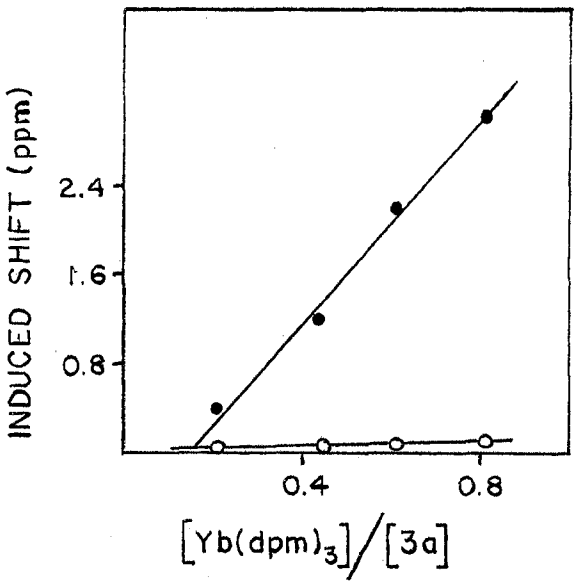


Figure 2. Ytterbium tris(2,2,6,6-tetramethylheptanedionate) induced shifts for the $CHCCl_3$ methine hydrogen of the major (○) and minor (●) epimers of acetal **3a**, in CCl_4 with [**3a**] = 0.4 *M*.

the corresponding chloral adducts, **41** was characterized by removal of the $CF_3CH<$ group with sodium in ether. Similar treatment of fluoral hemiacetals of secondary alcohols proved unsuccessful since, owing to the lower hemiacetal formation constants, fluoral was lost by degassing more rapidly than cyclization occurred.[25] For this reason and the difficulty we experienced (see Experimental Section) in storing and handling fluoral, no further work with fluoral hemiacetals was attempted.

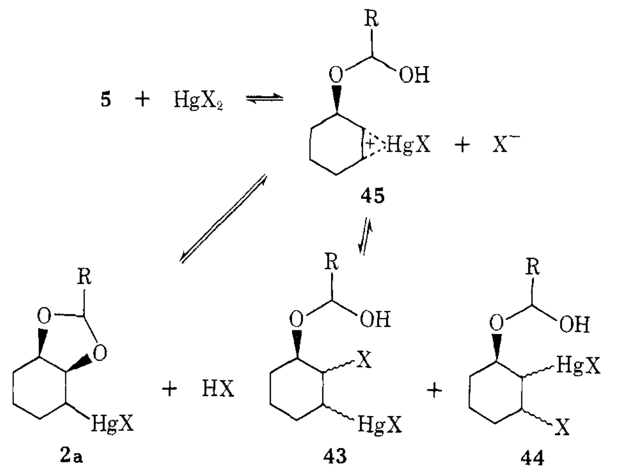
Although benzaldehyde does not readily form hemiacetal intermediates,[4] treatment of a benzaldehyde solution of **38** with mercuric trifluoroacetate for 140 hr, followed by reductive demercuration and purification by distillation and chromatography, afforded the cyclic 1,3-dioxane benzaldehyde adduct **42**[24] in 18% yield (crude yield 35%). Nmr experiments indicated that 40% of the starting alcohol **38** was bound as hemiacetal **40** under these conditions and this fact is undoubtedly responsible for the modest yield of adduct which was formed.

Discussion

Although the intermediacy of reversibly formed carbonyl addition intermediates (*e.g.*, hemiacetals) is well known in a variety of hydrolytic reactions,[26] this report constitutes one of few examples of their participation in stereospecific reactions of synthetic interest.[27] The two-step hemiacetal mediated hydration reaction described here is most useful for converting equatorial allylic cyclohexenols into the corresponding *cis*-1,2-diols. By this procedure **1a**, **1b**, and **10** are transformed in overall yields of 60–80%, and >99% isomeric purity, into the corresponding *cis*-1,2-diols **3a**, **3b**, and **12**, respectively. No alternate hydration method exhibits this high degree of regio- and stereospecificity. For example, the conventional oxymercuration–demercuration sequence is reported for **1a** to afford a mixture of all four possible diols with the major isomer (80%) being *trans*-1,3-cyclohexanediol and with the *cis*-1,2 isomer **4a** comprising only 1% of the isomer mixture.[28] Similarly, the corresponding *trans*-1,3-diol is reported to be the major product formed when **1b** is treated with mercuric acetate in $THF-H_2O$.[29]

For acyclic unsaturated alcohols the hemiacetal mediated hydration reaction shows little regiospecificity in THF. The reaction in benzene, however, is much more regiospecific. Even so the reaction appears of little synthetic use,

Scheme V



R = CCl_3; X = $OCOCF_3$

since the conventional oxymercuration–demercuration reaction is reported to afford equally high yields of the corresponding 1,3-diol. For example, Brown reports that 2-buten-1-ol is converted in 84% yield into a diol mixture containing 95% 1,3-butanediol by treatment with mercuric acetate in THF–H_2O.[30] The hemiacetal mediated reaction does, however, appear useful for hydration of homoallylic alcohols, since conventional oxymercuration–demercuration affords mainly cyclized tetrahydrofuran products.[17,30] In contrast, by the method reported here (*Z*)-3-hexen-1-ol is converted in 70% overall yield into a mixture of diols containing 91% 1,3-hexanediol.

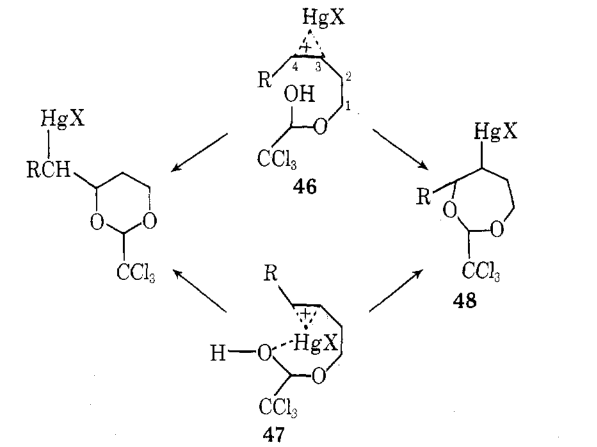
The mercuration–demercuration of chloral hemiacetals will in some cases be a useful route for preparing chloral acetals themselves. Acetals of chloral are not easy to prepare and have generally been synthesized by either the two-step route of eq 2[31] or in some cases from the direct

$$\underset{\displaystyle CCl_3}{ROCHOH} \xrightarrow{PCl_5} \underset{\displaystyle CCl_3}{ROCHCl} \xrightarrow{R'O^-} \underset{\displaystyle CCl_3}{ROCHOR'} \qquad (2)$$

acid-catalyzed condensation of alcohols with chloral.[32] The later method is most successful for 1,2- and 1,3-diols.[32] For example, **3a** was prepared in 43% yield from diol **4a** by this route.[9] Previous to this report no seven-membered ring chloral acetal, a 2-trichloromethyl-1,3-dioxepane, had been reported. Chloral acetals are useful intermediates for the preparation of dichloroketene acetals.[31c,32b]

The mechanism for the hemiacetal cyclization reaction which we prefer is illustrated for the case of 2-cyclohexen-1-ol in Scheme V. Addition of mercuric trifluoroacetate to hemiacetal **5** is postulated to form initially adducts **43** and **44** of which the kinetically preferred isomer should be **44** with X axial (trans to the oxygen atom at C-1).[28] These adducts are, however, formed reversibly and, if thermodynamically favored, capture at C-2 of an intermediate mercurinium ions, *e.g.*, **45** or its equivalent,[33] by the hemiacetal hydroxyl group to afford **2a** can ultimately dominate. This proposed mechanism follows from earlier reports by Brown and coworkers that in THF and other aprotic solvents adduct formation between an olefin and mercuric trifluoroacetate is both rapid and reversible.[13,34] The strongest evidence in favor of the proposed mechanism is the observed rapid disappearance of hemiacetal **5** when mercuric trifluoroacetate is added, and the corresponding slow build-up of the cyclic adduct **2a**. Consistent also with this mechanism is the observed cis stereochemistry of the cyclic chloromercuri adduct **32**.

Of particular mechanistic interest is the unprecedented kinetic preference for formation of the seven-membered ring 1,3-dioxepane adducts **27** and **28** when hemiacetals **22** and **24** are treated with mercuric trifluoroacetate in THF. Presumably these adducts do not result from external capture by the hemiacetal hydroxyl group of intermediate **46**,[33] since it is well established that kinetic formation of



six-membered rings is faster than that of seven-membered rings by several orders of magnitude.[35] Although the inductive effect of the hemiacetal group should, to some extent, favor nucleophilic addition at C-4,[30] it seems unlikely that this effect would be large enough to reverse the usual large kinetic preference for six-membered ring formation. One explanation for this unusual observation is that the hemiacetal hydroxyl group is not an external nucleophile, but rather is coordinated to mercury. Collapse of such an internally solvated intermediate, *e.g.*, mercurinium ion **47**, would not have the kinetic bias for six-membered ring formation expected of an external nucleophile and could result in formation of significant amounts of the seven-membered ring adduct **48**. The internal addition of anions in the coordination sphere of a solvated mercurinium ion intermediate has recently been suggested by Bach[19d] to account for the large amount of cis addition observed when bicyclo[2.2.2]octene is oxymercurated in nonpolar solvents. Studies aimed at clarifying this proposed mechanism for the case of the presumably analogous but simplier 5-alken-1-ols are in progress.

Experimental Section[36]

The solvents used were analytical reagent grade. No increase in yield resulted if THF was freshly distilled from $LiAlH_4$. Mercuric trifluoroacetate was prepared by Brown's procedure.[6a] 2-Cyclohexen-1-ol, (*E*)-2-hexen-1-ol, (*E*)-3-hexen-1-ol, (*Z*)-3-hexen-1-ol, (*E*)-3-hepten-1-ol, 2,4-hexadien-1-ol, and cinnamyl alcohol were purchased from Aldrich Chemical Co. or Chemical Samples Corp. *cis*- and *trans*-4-*tert*-butyl-*cis*-1,2-cyclohexanediol (**1b** and **1c**)[37] and 1-hydroxymethylcyclohexan-1-ol[1b] were prepared by literature procedures. 1,2α,4aβ,5,6,7,8,8aα-Octahydro-2-naphthol (**10**) was prepared from the isomeric axial alcohol[38] by oxidation[39] followed by reduction with $LiAlH_4$ at −78°. Authentic samples of aliphatic diols were prepared as follows: 1,3-hexanediol by $LiAlH_4$ reduction of ethyl 3-hydroxyhexanoate;[40] 1,4-hexanediol by hydroboration[41] of 1-hexen-4-ol; 1,3-heptanediol by hydroboration[41] of 1-hepten-3-ol; 1,4-heptanediol by hydroboration[41] of 1-hepten-4-ol. *cis*-1,2-Diols were prepared from the corresponding alkenes by the procedure of Woodward and Brutcher.[42] The diols were converted to the diacetates by treatment with acetic anhydride in pyridine and the diacetates were purified by preparative gc on a 5 ft × 0.25 in. column of 5% QF-1 on 60/80 Chromosorb B. For the determination of gc yields, internal standards (naphalene, *p*-dichlorobenzene, or diethyl adipate) were added to the crude reaction mixture before the isolation[36a] procedure.

Mercuration–Demercuration of Chloral Hemiacetal Derivatives of Cyclic Alcohols. *cis*-4-*tert*-Butyl-*cis*-1,2-(2-trichloromethylethylenedioxy)cyclohexane (3b). A mixture of **1b** (0.979 g, 6.36 mmol), chloral (1.3 ml, 13 mmol), and THF (20 ml) was

treated with mercuric trifluoroacetate (2.72 g, 6.36 mmol) and the resulting solution was stirred under nitrogen at room temperature for 48 hr. The solution was then cooled to 0° and reduced by adding 20 ml of 2.0 *M* NaOH, followed by 20 ml of 0.5 *M* sodium borohydride in 2.0 *M* NaOH. After stirring for 2 hr at 25°, the water layer was saturated with K_2CO_3 and the product was isolated[36a] with ether to afford 1.88 g of a white solid. Sublimation at 50° (0.1 Torr) yielded 1.20 g (74%) of **3b**, mp 84–88°, 99% pure by gc. Two singlets in the nmr spectrum at τ 4.77 and 4.87 in a 95:5 ratio indicated that this sample was a mixture of epimers at the CCl_3-bearing carbon.

The analytical sample was prepared by recrystallization from ethanol–water to afford white needles: mp 91.5–92.5°; ν_{max} (Nujol) 1133 (CO) and 803 cm^{-1} (CCl); nmr τ 4.77 (s, 1 H, $CHCCl_3$), 5.32–5.85 (m, 2 H, CHOR), 9.12 [s, 9 H, $C(CH_3)_3$].

Anal. Calcd for $C_{12}H_{19}O_2Cl_3$: C, 47.78; H, 6.35. Found: C, 47.84; H, 6.48.

***cis*-1,2-(2-Trichloromethylethylenedioxy)cyclohexane (3a).** In a similar manner a mixture of **1a** and chloral was treated for 60 hr with 1.0 equiv of mercuric trifluoroacetate to afford after distillation in 62% yield **3a**: bp 70–73° (0.1 Torr); ν_{max} (film) 1138 (CO) and 809 cm^{-1} (CCl); nmr ($CDCl_3$) τ 4.59 and 4.76 (singlets in 92:8 ratio, 1 H, $CHCCl_3$ epimers), 5.28–5.83 (m, 2 H, CHOR).

Crystallization from hexane at −78° afforded a pure sample of the major epimer, mp 32.0–34.5° (lit.[9] mp 34.5–35°).

Anal. Calcd for $C_8H_{11}Cl_3O_2$: C, 39.13; H, 4.52; Cl, 43.32. Found: C, 38.91; H, 4.31; Cl, 43.28.

Addition of ytterbium tris(2,2,6,6-tetramethylheptanedionate) [Yb(dpm)$_3$] to the epimer mixture resulted in shifts for the $CHCCl_3$ hydrogens shown in Figure 2.

1-Hydroxymethylcyclohexan-1-ol Trichloroacetaldehyde Acetal (8). In a similar manner a mixture of **7** and chloral was treated for 28 hr with 1.0 equiv of mercuric trifluoroacetate to afford after distillation in 71% yield **8**, bp 96–97° (0.5 Torr).

The analytical sample was prepared by preparative gc (5% SE-30): ν_{max} (film) 1342 (CO) and 812 cm^{-1} (CCl); nmr τ 4.80 (s, 1 H, $CHCCl_3$) and 6.20 (s, 2 H, CH_2OR).

Anal. Calcd for $C_9H_{13}O_2Cl_3$: C, 41.65; H, 5.05. Found: C, 41.55; H, 5.12.

Reductive cleavage of **8** with sodium in ether afforded in 96% yield diol **9** which was identical (ir, melting point, mixture melting point) with the diol obtained by conventional[38b] mercuration–demercuration of alcohol **7**.

1,2α,3α,4,4aβ,5,6,7,8,8aα-Decahydro-2,3-(2-trichloromethylethylenedioxy)naphthalene (11). In a similar manner a mixture of **10** (containing 80% of the equatorial hydroxyl isomer) and chloral was treated for 66 hr with 1.05 equiv of mercuric trifluoroacetate to afford after sublimation (70°, 0.1 Torr) in 67% yield (based on the equatorial isomer) **11**, mp 101–106°, 85% pure by gc.

The analytical sample was prepared by preparative gc (5% SE-30) and was recrystallized from hexane at −78°: mp 109.5–112°; ν_{max} (Nujol) 1338 (CO) and 808 cm^{-1} (CCl), 4.77 and 4.92 (singlets, 1 H total, $CHCCl_3$ epimers), and 5.13–5.80 (m, 2 H, CHOR).

Anal. Calcd for $C_{12}H_{17}Cl_3O_2$: C, 48.10; H, 5.72; Cl, 35.50. Found: C, 47.81; H, 5.51; Cl, 35.72.

Reduction of **11** with sodium in ether afforded in 85% yield diol **12**, which was identical (ir, melting point, mixture melting point) with an authentic sample[43] prepared[42] from *trans*-2-octalin.

Reductive Cleavage of Chloral Acetals. A. Cleavage of Acetal 3b with Sodium in Ether. Sodium dispersion (300 mg, 5.2 mmol, Alfa, 40% in mineral oil) was washed three times with hexane and added to a solution of **3b** (255 mg, 0.843 mmol) in anhydrous ether (15 ml). After stirring for 12 hr at 25°, the excess sodium was destroyed by carefully adding wet ether. Brine solution (20 ml) was added and the product was isolated[36a] with ether and crystallized (hexane–ether) to afford 137 mg (94%) of **4b**, mp 105–111°, 95% pure by nmr.

The analytical sample was prepared by two recrystallizations from CCl_4: mp 115–116.5°;[44] ν_{max} (KBr) 3400 cm^{-1} (OH); nmr ($CDCl_3$) τ 6.13 (m, 1 H, $W_{1/2}$ = 7.5 Hz, equatorial CHOH), 6.47 (m, 1 H, $W_{1/2}$ = 18 Hz, axial CHOH), 6.94 (broad s, 1 H, OH), 9.14 [s, 9 H, $C(CH_3)_3$].

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.90; H, 11.96.

B. Cleavage of Acetal 3a with Zinc and Acetic Acid. A mixture of **3a** (3.60 g, 14.6 mmol) and zinc dust (5.0 g, 76 mmol) in acetic acid (30 ml) was refluxed with stirring for 12 hr. The acetic acid was removed *in vacuo* and the product was isolated[36a] with ether to afford after distillation 2.18 g (75%) of *cis*-1,2-diacetoxycyclohexane, bp 72–73° (0.05 Torr), 95% pure by gc. Removal of the acetyl groups with NaOMe in methanol afforded after sublimation *cis*-1,2-cyclohexanediol (**4a**) in 85% yield, mp 96.5–98.5°, mmp 96–98° (lit.[48] 96–98°).

Mercuration–Demercuration of Hemiacetal Derivatives of Acyclic Alcohols. Cyclization of Hemiacetal 15. A mixture of (*E*)-2-hexen-1-ol (1.00 g, 10 mmol), chloral (2 ml, 20 mmol), and THF (10 ml) was treated at 25° with mercuric trifluoroacetate (4.28 g, 10 mmol). After 23 hr this solution was reductively worked up as described for **3b** to afford 2.4 g of a yellow oil. Bulb-to-bulb distillation afforded 1.93 g (79%) of a mixture of 4-*n*-propyl-2-trichloromethyl-1,3-dioxane (**18**) and 4-*n*-butyl-2-trichloromethyl-1,3-dioxolane (**21**), bp 70–76° (0.1 Torr). The nmr spectrum showed three $CCl_3CH<$ methine hydrogen singlets at τ 5.29, 4.79, and 4.72 in a 47:11:42 ratio. The peak at τ 5.29 is assigned to **18** by comparison with the nmr spectrum of the acetal mixture formed from **22**. An identical isomer ratio was observed at 6 hr.

Anal. Calcd for $C_8H_{13}Cl_3O_2$: C, 38.82; H, 5.29; Cl, 42.96. Found: C, 39.01; H, 5.43; Cl, 42.71.

The diacetate mixture obtained by reductive cleavage (Na) of this acetal mixture followed by acetylation is described in Table II.

Cyclization of Hemiacetal 22. In a similar manner a mixture of (*E*)-3-hexen-1-ol and chloral was treated with 1.0 equiv of mercuric trifluoroacetate. The build-up of the cyclic trichloroacetal was followed by gc and reached a maximum (44%) at 60 hr and began to slowly decline thereafter. Reductive work-up at 60 hr afforded in 32% yield a mixture of 4-*n*-propyl-2-trichloromethyl-1,3-dioxane (**18**) and 4-ethyl-2-trichloromethyl-1,3-dioxepane (**27**), bp 78–79° (0.2 Torr). The nmr spectrum showed two large CCl_3CH methine hydrogen singlets at τ 5.29 and 5.11 in a 53:47 ratio. At shorter reaction times (1–24 hr) four isomers were apparent: singlets at τ 5.29, 5.11, 5.18, and 5.07 in a 39:51:3:7 ratio. The major peaks at τ 5.29 and 5.11 are assigned to **18** and **27**, respectively.

Anal. Calcd for $C_8H_{13}Cl_3O_2$: C, 38.82; H, 5.29. Found: C, 39.15; H, 5.50.

The mixture of diacetates obtained by reductive cleavage (Na) of the kinetic acetal mixture (9 hr) followed by acetylation is described in Table II. The gc assignment was confirmed by isolation of the 1,3- and 1,4-diacetoxyhexanes by preparative gc (10% QF-1) and comparison (ir and nmr) with authentic samples.

Cyclization of Hemiacetal 23. In a similar manner (*Z*)-3-hexen-1-ol and chloral were treated for 48 hr with 1.0 equiv of mercuric trifluoroacetate to afford after distillation a mixture of **18** and **27** in 72% yield, bp 76–78° (0.1 Torr). The nmr spectrum showed singlets at τ 5.29 and 5.11 in a ratio of 65:35 for **18** and **27**, respectively. The isomer ratio was identical at 22 hr.

The mixture of diacetates obtained by reductive cleavage of this acetal mixture followed by acetylation is described in Table II.

Cyclization of Hemiacetal 24. In a similar manner (*E*)-3-hepten-1-ol and chloral were treated for 48 hr with 1.05 equiv of mercuric trifluoroacetate to afford, after distillation, in 45% yield a mixture of 4-*n*-butyl-2-trichloromethyl-1,3-dioxane (**26**) and 4-*n*-propyl-2-trichloromethyl-1,3-dioxepane (**28**). The nmr spectrum showed two trichloromethyl methine hydrogen singlets at τ 5.30 and 5.12 in a 60:40 ratio. Since at 6 hr the ratio of these peaks is 40:60 (50:50 at 24 hr), the τ 5.30 peak is assigned to **26** and the τ 5.12 peak to **28**.

The mixture of diacetates obtained by reductive cleavage (Na) of this acetal mixture followed by acetylation is described in Table II.

Cyclization of Hemiacetal 17. In a similar manner 2,4-hexadien-1-ol (a mixture of isomers) was treated with 1.0 equiv of mercuric trifluoroacetate for 48 hr to afford after distillation 4-propenyl-2-trichloromethyl-1,3-dioxane (**20**) in 37% yield, bp 70–74° (0.1 Torr). The nmr spectrum showed one major absorption for the $>CHCCl_3$ methine hydrogen at τ 5.20.

Hydrogenation (Pd/C) followed by reductive cleavage (Na) and acetylation afforded the mixture of diacetates described in Table II.

Cyclization of Hemiacetal 40. A solution of (*E*)-2-hexen-1-ol (1.06 g, 10.6 mmol), benzaldehyde (25 ml, 245 mmol), mercuric trifluoroacetate (4.53 g, 10.6 mmol), and THF (10 ml) was stirred under nitrogen for 6 days at 25°. Demercuration as described for **3b** and isolation[36a] with ether afforded the crude acetal, which was dissolved in dry THF and reduced with $LiAlH_4$ (to convert any benzaldehyde to benzyl alcohol). Distillation afforded 2-phenyl-4-*n*-propyl-1,3-dioxane (**42**), bp 73° (0.01 Torr).

The analytical sample was prepared by preparative tlc on silica

gel using hexane–ethyl acetate (9:1) as eluent: ν_{max} (film) 1105 (CO), 749, and 696 cm^{-1}; nmr τ 2.4–2.9 (m, 5 H, C_6H_5), 4.68 (s, 1 H, >CHPh), and 5.4–6.5 (m, 3 H, CHOR).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 76.06; H, 8.35. Found: C, 76.00; H, 8.54.

Hydrolysis with 1 *M* HCl in refluxing THF–H_2O followed by acetylation afforded 1,3-diacetoxyhexane (94%) contaminated with 6% or 1,2-diacetoxyhexane.

Cyclization of Hemiacetal 39. A solution of trifluoroacetaldehyde[49] (20 ml, 0.9 *M*) in ether at −78° was treated with (*E*)-2-hexen-1-ol (0.929 g, 9.3 mmol). Upon warming to room temperature excess fluoral was lost by degassing and the nmr spectrum showed a complex multiplet centered at τ 5.2 for the >$CHCF_3$ methine hydrogen of **39**. Mercuric trifluoroacetate (4.28 g, 9.3 mmol) was added and the solution was maintained at 25° for 90 hr and demercurated as described for **3b**. Isolation[36a] with ether afforded 1.207 g (52%, 80% pure by gc) of crude 4-*n*-propyl-2-trifluoromethyl-1,3-dioxane (**41**). The nmr spectrum indicated the predominant formation of a single cyclic acetal isomer, as only one quartet centered at τ 5.25 [$J(^{19}F\text{-}H)$ = 3.5 Hz] was observed for the >$CHCF_3$ methine hydrogen. At shorter reaction times (24–36 hr) two isomers were apparent—quartets centered at τ 5.25 and 4.87 in a ratio of 85:15. Preparative gc (5% QF-1) afforded **41** (96% pure by gc): ν_{max} (film) 1299 and 1183 cm^{-1} (CF); nmr τ 5.25 (q, 1 H, $CHCF_3$, J = 3.5 Hz) and 3.9 (m, 3 H, CHOR).[53]

Reductive cleavage of **41** with sodium in ether followed by acetylation afforded 1,3-diacetoxyhexane (96%) contaminated with 4% of 1,2-diacetoxyhexane.

***cis*-3-Chloromercuri-*cis*-1,2-(2-trichloromethylethylenedioxy)cyclohexane (32).** A solution of **1a** (1.96 g, 20 mmol), chloral (4.0 ml, 40 mmol), and mercuric trifluoroacetate (9.32 g, 22 mmol) in THF (20 ml) was stirred for 48 hr at 25°. The addition of 10% sodium chloride solution (40 ml) produced an oily precipitate, which was isolated[36a] with $CHCl_3$ to afford 6.4 g of a white semisolid (70% **32** by nmr). Crystallization from ethanol–H_2O and recrystallization from 1:1 ethanol–hexane afforded 1.56 g (16%) of **32**, mp 142.5–143.5°.

The analytical sample was prepared by two recrystallizations from benzene to afford fine white needles: mp 142.5–144°; ν_{max} (Nujol) 1131 (CO) and 830 cm^{-1} (CCl); nmr ($CDCl_3$) τ 4.53 (s, 1 H, $CHCCl_3$), 5.05–5.60 (m, 2 H, CHOR), 7.23 (m, 1 H, $W_{1/2}$ = 19 Hz, axial CH-HgCl).

Anal. Calcd for $C_8H_{10}O_2Cl_4Hg$: C, 19.99; H, 2.10. Found: C, 20.17; H, 1.89.

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Registry No.—**1a**, 822-67-3; **1b**, 26819-49-8; **3a** α epimer, 51014-77-8; **3a** β epimer, 51014-78-9; **3b** α epimer, 51014-79-0; **3b** β epimer, 51014-80-3; **4a**, 1792-81-0; **4b**, 19793-86-3; **7**, 4845-04-9; **8**, 39257-35-7; **10**, 18314-48-2; **11** α epimer, 51014-81-4; **11** β epimer, 51096-40-3; **15**, 51014-82-5; **17**, 51015-02-2; **18**, 51015-03-3; **20**, 51015-04-4; **21**, 51015-05-5; **22**, 51014-83-6; **23**, 51014-84-7; **24**, 51014-85-8; **26**, 51022-61-8; **27**, 51022-62-9; **28**, 51015-06-6; **32**, 51015-07-7; **39**, 51014-86-9; **40**, 51014-87-0; *cis*-**41**, 51014-88-1; *trans*-**41**, 51014-89-2; **42**, 51015-08-8; chloral, 75-87-6; mercuric trifluoroacetate, 1600-27-7; *cis*-1,2-diacetoxycyclohexane, 2396-76-1; (*E*)-2-hexen-1-ol, 928-95-0; (*E*)-3-hexen-1-ol, 928-97-2; (*Z*)-3-hexen-1-ol, 928-96-1; (*E*)-3-hepten-1-ol, 2108-05-6; 2,4-hexadien-1-ol, 111-28-4; benzaldehyde, 100-52-7; trifluoroacetaldehyde, 75-90-1.

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(1) Examples include (a) epoxidation, H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 4608 (1957); M. M. Canet, *Bull. Soc. Chim. Fr.*, 3853 (1966); J. A. Marshall and A. E. Greene, *J. Org. Chem.*, **36**, 2035 (1971); R. Zurflüh, E. N. Wall, J. B. Sidall, and J. A. Edwards, *J. Amer. Chem. Soc.*, **90**, 6224 (1968); K. B. Sharpless and R. C. Michaelson, *ibid.*, **95**, 6136 (1973); (b) methylene transfer, J. H.-H. Chan and B. Rickborn, *ibid.*, **90**, 6406 (1968); W. C. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963); (c) hydride additions, W. T. Borden, *ibid.*, **92**, 4898 (1970); (d) organolithium additions, D. J. Cram and D. R. Wilson, *ibid.*, **85**, 1245 (1963); H. Felkin, G. Swierczewski, and A. Tambute, *Tetrahedron Lett.*, 707 (1969); (e) Grignard addition, E. Ghera, *Chem. Commun.*, 398 (1971); (f) hydrogenation, T. J. Howard, *Chem. Ind. (London)*, 1899 (1963); (g) Claisen-type rearrangements, G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 2091, 2095 (1967); W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. T. Lee, D. J. Faulkner, and M. R. Peterson, *J. Amer. Chem. Soc.*, **92**, 741 (1970); A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964).

(2) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapters 1–3.

(3) For a preliminary report of a portion of this work see L. Overman, *J. Chem. Soc., Chem. Commun.*, 1196 (1972).

(4) *Cf.* P. LeHénaff, *Bull. Soc. Chim. Fr.*, 4687 (1968), and references cited therein.

(5) In CCl_4 this hydrogen appears as a singlet for all the secondary alcohols we have studied and indicates that the equilibrium of eq 1 is faster than the nmr time scale, since two diastereoisomers are possible. In basic solvents such as THF this hydrogen appears as an unresolved multiplet which we take to indicate that not only is the equilibrium of, *e.g.*, eq 1 slower in such a hydrogen-bonding solvent but also that coupling of the methine hydrogen to the hydroxyl group is observed. As expected this multiplet collapses to a singlet upon the addition of trifluoroacetic acid.

(6) (a) H. C. Brown and M.-H. Rei, *J. Amer. Chem. Soc.*, **91**, 5646 (1969); (b) H. C. Brown and J. T. Kurek, *ibid.*, **91**, 5647 (1969); (c) H. C. Brown, P. J. Geoghegan, Jr., G. L. Lynch, and J. T. Kurek, *J. Org. Chem.*, **37**, 1941 (1972).

(7) (a) For a thorough review of the literature for the oxymercuration reaction through 1950, see J. Chatt, *Chem. Rev.*, **48**, 7 (1951). Various recent aspects of the reaction have been reviewed; (b) N. S. Zefirov, *Russ. Chem. Rev.*, **34**, 527 (1965); (c) W. Kitching, *Organometal Chem. Rev.*, **3**, 61 (1968); (d) L. G. Makarova and A. N. Nesmeyanov, "Methods of Elemento-organic Chemistry: The Organic Compounds of Mercury," Vol. 4, North-Holland Publishing Co., Amsterdam, 1967.

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Pyrolysis of Amino Acids. Mechanistic Considerations

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Pyrolysis (*ca.* 500°) of a number of structurally different amino acids has been studied to determine the effects on mechanisms and product distribution exerted by geometrical isomerism. Aliphatic protein amino acids decompose predominantly by decarboxylation and condensation reactions as primary steps. β-Amino acids lose ammonia to give unsaturated acids. α-Amino acids containing α-alkyl substituents undergo a novel SNi reaction losing ammonia and forming an intermediate α-lactone that subsequently yields a ketone upon decarbonylation. γ- and δ-amino acids give 2-pyrrolidinone and 2-piperidone, respectively, as major pyrolysis products. The ε-amino acid, while producing some lactam, yields several chain-shortened amines and nitriles with no single predominant product.

The use of pyrolysis for the analysis of complex molecules and polymers has grown steadily in recent years. Modern techniques utilize pyrolysis methods in conjunction with gas chromatography (gc) and mass spectrometry (ms) or, in many instances, both for the analysis of complex systems.

Applications are increasingly growing in the fields of synthetic polymers[2] and biological research.[3] Pyrolysis has been used to study nucleotides,[4,5] mycolic acid,[6] steroids,[7] and acetycholine,[8] and for amino acid[9] and peptide identification.[10]

Recently, the field has grown to include attempts to characterize strains or species of microorganisms by pyrolysis coupled with gc, ms, and gc–ms.[11,12] While the use of this technique for analytical purposes is possible without a detailed understanding of the mechanisms involved, the full potential for pyrolysis can only be realized when the fragmentation products can be related to starting materials *via* logical mechanisms.

One important class of compounds is the amino acids. In addition to their obvious biological significance, a suite of amino acids has been found in the Murchison[13,14] and Orgueil[15] meteorites that are considered to be of extraterrestrial origin. Since NASA plans to include a pyrolysis gc–ms experiment aboard a Viking spacecraft (scheduled to land on Mars in mid-1976), a knowledge of thermally induced fragmentation processes of this apparently important class of compounds would assist the interpretation of any results forthcoming from that experiment.

We have previously reported on the thermal fragmentation of a selected group of protein amino acids.[16] Our studies have been expanded to include additional homologs to that series and labeled substrates which provide evidence for the mechanisms proposed. In addition, a variety of positional isomeric monoamino monocarboxylic acids have been investigated. From these data, a more consistent scheme can be developed to describe the pathways by which amino acids thermally decompose.