Acid-Catalyzed Disproportionation Reactions of Aliphatic Ketones. Scope and Mechanism[1a]

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Upon treatment with perchloric acid, straight-chain aliphatic ketones disproportionate, in low yields, to straight-chain (but not to branched-chain) ketones of both higher and lower carbon number. This reaction appears to be general for straight-chain ketones, but does not occur for α-branched ketones. The proposed mechanism involves an aldol condensation, dehydration of the aldol conjugate acid to a carbonium ion, alkyl or hydrogen shifts in the carbonium ion, rehydration to an isomeric aldol, and reverse aldolization to rearranged ketones and/or aldehydes. Support for the mechanism was obtained by (1) carrying out product studies on simple ketones, (2) following the paths of olefinic ketones which were independently synthesized and which lead to proposed intermediate carbonium ions, and (3) identifying rearranged olefinic ketones and rearranged dihydrofurans. Dihydrofurans are readily formed from olefinic ketones under the reaction conditions in sufficient yields to show synthetic promise. Apparently, a relatively facile oxygen function rearrangement also occurs in ethyl and propyl straight-chain olefinic ketones.

Most of the many investigations of acid-catalyzed rearrangements of aldehydes and ketones to isomeric ketones can be rationalized on the basis of intramolecular mechanisms[2] involving alkyl and/or oxygen function shifts in the conjugate acids of the carbonyl compounds. Formally, the net result of all these intramolecular mechanisms is the exchange of a group attached directly to the carbonyl carbon with a group attached to the α carbon on the other side of the carbonyl carbon.[3]
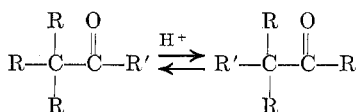
In the course of a detailed study of the mechanisms of these rearrangements, it was discovered[4] that ketones of molecular weight both higher and lower than the starting material were formed. For instance, butanone forms acetone, 2-pentanone, 3-pentanone, 3-hexanone, and numerous other nonketonic compounds. A generalized form of the working hypothesis mechanism given by Ookuni and Fry[4] for this disproportionation reaction is given below.

$$R_1COCHR_2R_4 + R_3COR_5$$

R_1, R_4 and R_5 = alkyl; R_2 and R_3 = alkyl or hydrogen
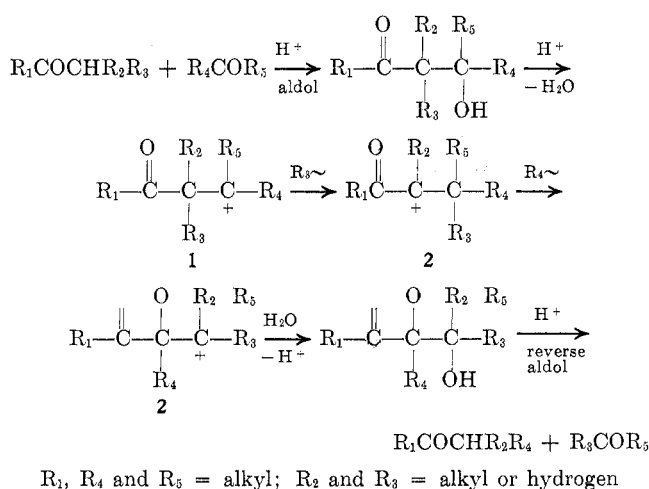
(Other paths would lead to products with other combinations of R_2, R_3, R_4, and R_5.)

This mechanism involves an aldol condensation, dehydration of the aldol conjugate acid to a carbonium ion, alkyl or hydrogen shifts in the carbonium ion, rehydration to an isomeric aldol, and reverse aldolization to rearranged ketones and/or aldehydes. This bimolecular path for the ketone disproportionation reaction is similar to the bimolecular path established for rearrangements in the reactions of alkyl halides with acids.[5]

The report of the discovery of the disproportionation reaction[4] mentioned only straight-chain aliphatic ketones. However, from the mechanism suggested, there was no immediately obvious reason why branched-chain ketones should not undergo the disproportionation reaction, or why branched-chain compounds should not be obtained from straight-chain starting materials. For instance, two molecules of 2,4-dimethyl-3-pentanone (R_1 = R_4 = R_5 = isopropyl; R_2 = R_3 = methyl) might disproportionate to 2,4,5-trimethyl-3-hexanone and 3-methyl-2-butanone, and two molecules of butanone (R_1 = R_2 = R_4 = methyl; R_3 = H; R_5 = ethyl) might disproportionate to 3-methyl-2-butanone and propionaldehyde (or, with R_1 = R_2 = R_5 = methyl, R_3 = H, and R_4 = ethyl, to 3-methyl-2-pentanone and acetaldehyde). Accordingly, careful searches were made for disproportionation products in the reactions of branched-chain compounds, and for branched-chain products from straight-chain starting materials.

Another major effort in studying the mechanism of the disproportionation reaction was the investigation of the products formed by introduction into the reaction system of the proposed intermediate carbonium ions 1, 2, or 3 by independent paths. These carbonium ions would be expected to form by perchloric acid treatment of independently synthesized, appropriately substituted olefinic ketones. If the simple ketones at both ends of

(1) (a) Supported by U. S. Atomic Energy Commission Contract AT-(40-1)-3234; taken in part from the Ph.D. Dissertations of D. D. F. and W. H. C.; presented in part at the Southwest Regional American Chemical Society Meeting, Albuquerque, N. M., Dec 2, 1966. (b) Texas Eastman Fellow, 1964-1965. (c) Monsanto Fellow, 1963-1964.

(2) For a summary of the proposed mechanisms and leading references to these investigations, see W. H. Corkern and A. Fry, *J. Amer. Chem. Soc.*, **89**, 5888 (1967).

(3) It should be noted that this result is accomplished by interchange of R and R', or, alternatively, oxygen may interchange with two R groups (oxygen function rearrangement).

(4) I. Ookuni and A. Fry, *Tetrahedron Lett.*, 989 (1962).

(5) G. J. Karabatsos, F. M. Vane, and S. Meyerson, *J. Amer. Chem. Soc.*, **83**, 4297 (1961); **85**, 733 (1963); G. J. Karabatsos and F. M. Vane, *ibid.*, **85**, 729 (1963).

TABLE I

SCOPE OF THE DISPROPORTIONATION REACTION

Reactant	Isolated products	Glpc-identified products	Products sought but not found
Acetone		Butanone[a]	
Butanone	2-Pentanone 3-Pentanone	Acetone[b] 3-Hexanone	Acetaldehyde Propionaldehyde MeCOCHMe₂ MeCOCHMeEt
3-Pentanone	2-Pentanone[c] 3-Hexanone	Acetone (trace)[d,e] Butanone 2-Hexanone (trace)[e]	EtCOCHMeEt
4-Heptanone		3-Hexanone 4-Octanone (?)	
Propiophenone	Butyrophenone PhCH₂COMe[c]	Acetophenone[f]	
MeCOCHMe₂			Acetone Isobutyraldehyde MeCOCHMeCHMe₂ Me₂CHCOEt
Me₂CHCOEt	MeCOCHMeEt[c]		Butanone MeCOCHMe₂ MeCOCH₂CHMe₂[c]
Me₂CHCOCHMe₂	MeCOCHMeCHMe₂[c]		MeCOCHMe₂

[a] 4-Methyl-3-penten-2-one (mesityl oxide) (5), the aldol condensation product dehydration product, was also identified. [b] Aldol dehydration products *cis*- (6) and *trans*-3,4-dimethyl-3-hexen-2-one (7), *cis*- (8) and *trans*-3,4-dimethyl-4-hexen-2-one (9), and *cis*- (10) and *trans*-5-methyl-4-hepten-3-one (11) were also identified, and *cis*- (12) and *trans*-2,3,4,5-tetramethyl-4,5-dihydrofuran (13) were isolated. In an experiment with 2-butanone-1-¹⁴C in 70% perchloric acid for 48 hr at 50°, added holdback carriers of acetone, 2-pentanone, 3-pentanone, and 3-hexanone, after reisolation and derivative preparation, all showed the presence of radioactivity. [c] Intramolecular rearrangement product. [d] Aldol dehydration products *cis*- (14) and *trans*-5-ethyl-4-methyl-5-hepten-3-one (15) were also identified, and *cis*- (16) and *trans*-2,4-diethyl-3,5-dimethyl-4,5-dihydrofuran (17) were isolated. [e] Disproportionation product derived from the 2-pentanone formed by intramolecular rearrangement of 3-pentanone; the 2-hexanone might also arise from oxygen function rearrangement of 3-hexanone. [f] F. E. Juge, Jr., private communication; methyl benzyl ketone was obtained in gross amounts, butyrophenone was isolated by preparative glpc and identified by spectral and derivative comparisons, and acetophenone was identified by glpc retention times on several columns.

the above mechanistic path were formed, the mechanism would be supported.

$$R_1\!-\!\overset{\overset{\text{O}}{\|}}{C}\!-\!\overset{\overset{R_3}{|}}{C}\!=\!\overset{\overset{R_5}{|}}{C}\!-\!R_4$$

4

↓↑ H⁺

$$R_1\!-\!\overset{\overset{\text{O}}{\|}}{C}\!-\!\overset{\overset{R_3}{|}}{\underset{\underset{H}{|}}{C}}\!-\!\overset{\overset{R_5}{|}}{\underset{+}{C}}\!-\!R_4 \xrightarrow[\text{aldol}]{\text{reverse}} R_1COCH_2R_3 + R_4COR_5$$

1, R₂ = H

↓ R₃~

2, R₂ = H

↓ R₄~

$$R_1\!-\!\overset{\overset{\text{O}}{\|}}{C}\!-\!\overset{\overset{R_4}{|}}{\underset{\underset{H}{|}}{C}}\!-\!\overset{\overset{R_5}{|}}{\underset{+}{C}}\!-\!R_3 \xrightarrow[\text{aldol}]{\text{reverse}} R_1COCH_2R_4 + R_3COR_5$$

3, R₂ = H

(Other paths would lead to products with other combinations of R₂, R₄, and R₅.)

Results and Discussion

The experiments on the scope of the disproportionation reactions of straight-chain and branched-chain aliphatic ketones are summarized in Table I. All straight-chain aliphatic ketones studied formed detectable amounts of disproportionation products. No branched-chain disproportionation products were obtained from straight-chain compounds. No aldehydes were detected as disproportionation products. (It is very likely that aldehydes were formed, but, being highly reactive, condensed immediately to polymeric materials; when aldehydes were subjected to the reaction conditions, no simple aldehydes were recovered.) The disproportionation reaction appears to be general for, but restricted to, the production of straight-chain aliphatic ketones from other straight-chain aliphatic ketones.[6]

The reactions of the straight-chain ketones to give straight-chain disproportionation products may be classified into three groups: (1) reactions in which $R_2 = H$ and $R_3 =$ alkyl, so that the sequence $1 \rightarrow 2 \rightarrow 3$ involves tertiary → secondary → tertiary carbonium ions; (2) reactions in which $R_2 = R_3 = H$, so that $1 \rightarrow 2 \rightarrow 3$ involves tertiary → secondary → secondary carbonium ions; and (3) reactions which must involve preliminary intramolecular rearrangements followed by group 1 and/or 2.

All of the reactions giving products which were in high enough yields to be isolated are in group 1, with the exception of the formation of 3-pentanone from butanone. The lower yields of the products in the other two groups is what would be expected on the basis of reversible reactions, taking into account the greater stability of tertiary compared with secondary carbonium ions, and the difficulty of formation of products by paths involving sequential intramolecular and intermolecular reactions. The relatively large yield of 3-pentanone

(6) If the chain branching is remote from the carbonyl group, disproportionation reactions would no doubt occur.

from butanone is almost certainly due to a large contribution from intramolecular rearrangement of the first-formed 2-pentanone, added to a smaller amount formed by a tertiary → secondary → secondary carbonium ion path. Furthermore, the formation of 2-pentanone starting from 3-pentanone must be intramolecular,[7] and the 2-hexanone and acetone observed in the long-time 3-pentanone reactions must be derived from the 2-pentanone by condensation with itself or with 3-pentanone, or, for 2-hexanone, from an oxygen function rearrangement of 3-hexanone.

The yields in all of these disproportionation reactions are very low, and it is clear that the reaction has no synthetic value. There is considerable mechanistic significance, however, since the results are quite striking. The low yields are readily understandable on the basis of carbonium ion stabilities and the existence of more favorable competing reaction paths. One would not expect tertiary ion 1 to rearrange readily to secondary ion 2 where the positive center is adjacent to a carbonyl carbon. Furthermore, the rearrangement must always compete with the formation of dihydrofurans (see below) and with the normal reverse aldol reaction. Considerable attention is given to the matter of relative yields in the Experimental Section.

In order for branched-chain disproportionation products to be formed from straight-chain ketones, the sequence 1 → 2 → 3 would need to involve a tertiary → tertiary → secondary carbonium ion path, the last step of which is unlikely in itself, but which is made doubly unattractive by the necessity for both R_2 and R_4 in 3 to be alkyl groups, resulting in serious steric crowding adjacent to the carbonyl group. This matter will be covered further in the olefinic ketone discussion below.

The inability of branched-chain ketones to give the disproportionation reaction is probably due to a variety of factors: (1) the competition of more favorable intramolecular processes leading to rearranged isomeric ketones (for instance, 2-methyl-3-pentanone rearranges readily to 3-methyl-2-pentanone); or (2) the favorable competition of paths leading to dihydrofurans from 2 (see below); or (3) the failure of initial aldol condensation for cases where R_2 and R_3 are both alkyl (again, there would be excessive steric crowding adjacent to the carbonyl group). It is known,[8] for example, that in acid solution 3-methyl-2-butanone condenses almost exclusively at the methyl carbon.

The strongest support for the proposed mechanism is given by the results of the experiments with externally synthesized olefinic ketones. In several cases (see Table I, footnotes *a*, *b*, and *c*), the olefinic ketones expected aldol dehydration products were shown to be present in the simple ketone–perchloric acid reaction system. Perchloric acid treatment of a series of olefinic ketones of this type resulted in the formation of both the unrearranged and rearranged simple ketones, as summarized in Table II.

In all of these cases, in the general olefinic ketone formula 4, R_4 and R_5 are alkyl groups, and the rearrangement sequence 1 → 2 always involves alkyl or hydrogen migration to a tertiary carbonium ion center, giving a secondary carbonium ion. Further rearrangement of 2

(7) A. Fry and W. H. Corkern, *J. Amer. Chem. Soc.*, **89**, 5894 (1967).
(8) W. H. Corkern, Ph.D. Dissertation, University of Arkansas, 1966, p 149.

TABLE II

SIMPLE KETONIC PRODUCTS FROM THE REACTIONS OF
OLEFINIC KETONES WITH PERCHLORIC ACID

Compd	Reverse aldol products	Rearranged ketones
Me₂C=CHCOMe (5)	Acetone	Butanone
EtMeC=CMeCOMe, *cis*- (6) and *trans*- (7)	Butanone	Acetone 2-Pentanone
EtMeC=CHCOEt, *cis*- (10) and *trans*- (11)	Butanone	3-Pentanone 3-Hexanone
Et₂C=CMeCOEt (18)	3-Pentanone	Butanone 3-Hexanone
n-PrMeC=CHCO-*n*-Pr, *cis*- (19) and *trans*- (20)	2-Pentanone	3-Hexanone
Me₂C=CEtCOMe (21)	Acetone 2-Pentanone	Butanone
Me₂C=CHCOEt (22)	Acetone Butanone	3-Pentanone
Me₂C=CHCO-*n*-Pr (23)	Acetone 2-Pentanone	3-Hexanone
MeCH=CMeCHEtCOEt (24)	Butanone 3-Hexanone	3-Pentanone

to 3 gives a secondary or tertiary carbonium ion, which reverts to the rearranged aldol decomposition products. The proposed pathway would be strongly supported if olefins derived from type 3 ions could be detected, and a careful search was made for them for the cases listed in Table II. None could be detected, so a more favorable case was sought.

It was thought that the steady-state equilibrium of the intermediate rearranged olefinic ketone might be large enough to detect if the initial migration (1 → 2) were to the more favorable (more highly localized positive charge) secondary carbonium ion. Two such cases were tried. The rearranged olefinic ketones were detected in both cases, along with the rearranged and unrearranged simple ketones.
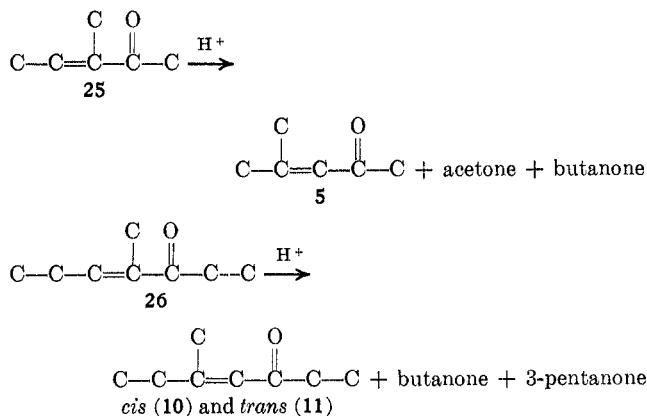
The rearrangement of 25 and 5 takes place to a considerable extent, as shown by the presence of 12% acetone in the acetone–butanone fraction recovered from the reaction of 25 with perchloric acid.

These two examples provide convincing evidence for intermediates throughout the reaction scheme, and hence strongly support the proposed mechanism.

In the original paper on the ketone disproportionation reaction[4] it was reported that unidentified volatile compounds were produced. These compounds have been characterized as dihydrofuran derivatives and, in fact, are the major volatile products of the reaction of aliphatic ketones with perchloric acid. For example, butanone reacts to give *cis*- (12) and *trans*-2,3,4,5-tetra-

methyl-4,5-dihydrofuran (**13**). It has been found that these compounds are readily produced from the reaction of the aldol condensation–dehydration product of butanone, 3,4-dimethyl-4-hexen-2-one (**8** and **9**), with perchloric acid, and somewhat more slowly from the conjugated isomer, 3,4-dimethyl-3-hexen-2-one (**6** and **7**). On the basis of these results the formation of dihydrofurans from simple ketones can be represented by the following reactions.
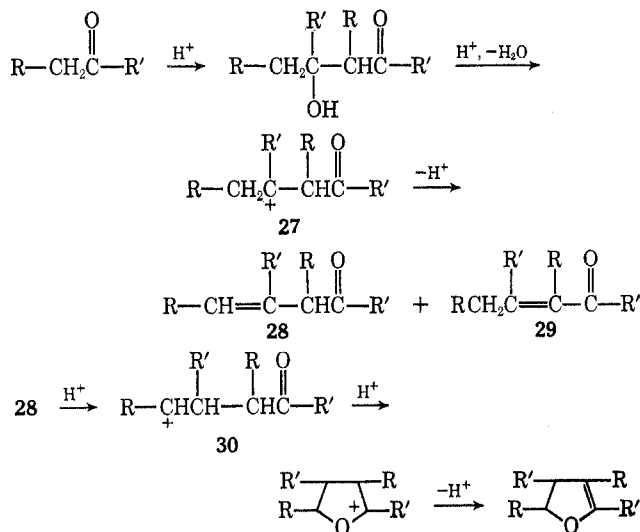

Intermediate **30** could also be formed *via* a hydride shift in **27** which, of course, is a precursor of **28** and **29**.

The fact that dihydrofuran derivatives are readily formed from some olefinic ketones was used to advantage in the mechanistic investigation. For example, olefinic ketones **14** and **15** readily react with perchloric acid to give dihydrofurans **16** and **17**. These olefinic ketones and dihydrofurans were also found in the 3-pentanone–perchloric acid reaction mixture.
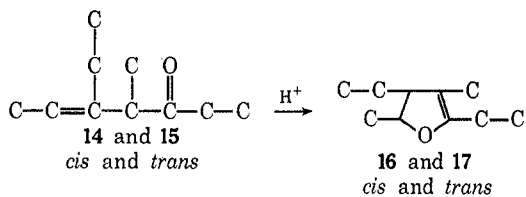
Compound **18**, the conjugated isomer of **14** and **15**, gives dihydrofurans **16** and **17** somewhat more slowly, in addition to giving the rearrangement reaction.
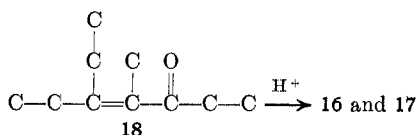
Also, of considerable mechanistic significance, in the disproportionation reaction of **18**, rearranged dihydrofurans **31** and **32** are formed, presumably as follows.
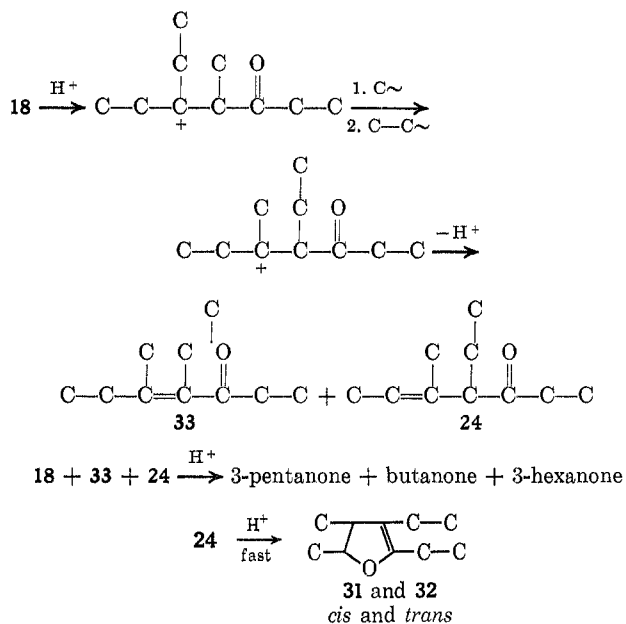
In a similar reaction, olefinic ketone **21** gave **12** and **13**.
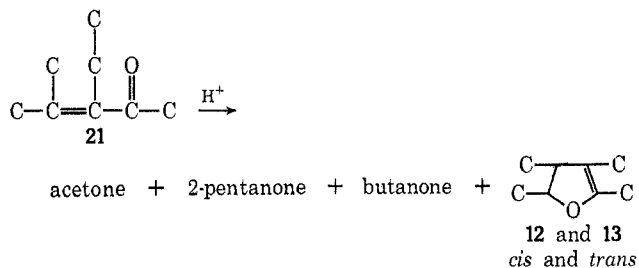
Here, dihydrofurans **12** and **13** are rearranged products formed in a reaction analogous to the one described in detail above. These two compounds are the primary products formed in the reaction of butanone with perchloric acid and in the reaction of 3,4-dimethyl-4-hexen-2-one (**8** and **9**) (an aldol condensation–dehydration product of butanone) with perchloric acid.

The above results demonstrate conclusively that rearranged olefinic ketones and dihydrofurans are formed from the aldol condensation–dehydration products; that these rearranged olefinic ketones decompose to the observed disproportionation products; and that the rearranged olefinic ketones also revert to the simple ketones from which the initial aldol condensation products were derived. These facts support the proposed mechanism for the disproportionation reaction very strongly.

Under conditions mild enough to prevent extensive polymerization, the main reaction of simple aliphatic ketones and olefinic ketones with perchloric acid is the formation of dihydrofuran derivatives. Dihydrofuran formation from olefinic ketones (particularly β,γ-unsaturated ketones) is faster than from the simple ketones, and this reaction may be of general synthetic utility.
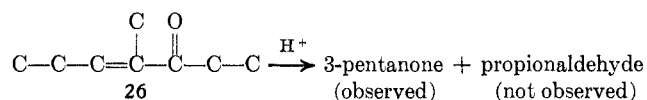
Reactions of olefinic ketones provide an additional and perhaps more critical test of the possibility that branched-chain ketones might be formed from straight-chain starting marerials. The formation of 3-pentanone from **10** and **11** (Table II) involves a hydride transfer followed by a methyl migration. If this occurs it might be expected that **6** and **7**, for example, would

show a hydrogen–methyl interchange to lead to 3-methylbutanone; however, this compound could not be detected. (The possibility that intermediate **34** could cleave at the β,γ bond was considered; however, no 3,3-dimethylbutanone could be found in this reaction.)
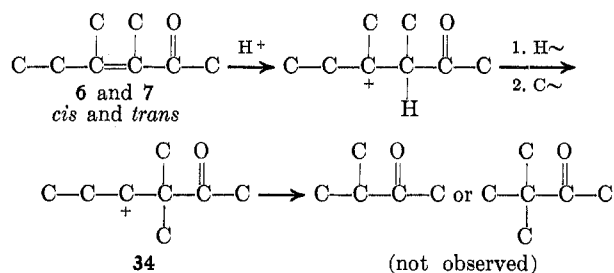
It is seen that the loss of a proton from intermediate **34** can lead only to the nonconjugated ketone. It is known that nonconjugated ketones readily react with perchloric acid to give dihydrofurans. Possibly, this occurs with intermediate **34** if the indicated migrations actually take place. However, as mentioned earlier, it is probable that the steric compression of attaching three alkyl groups on one of the carbons α to the carbonyl group is too great to permit appreciable reaction through such an intermediate.

The work with olefinic ketones also sheds some light on the question of aldehyde formation in the disproportionation reaction. For some of the reaction paths leading to rearranged ketones, aldehydes would be the other rearrangement product, but none have been found (Table I). This observation is thought to be due to the fact that aldehydes disappear (polymerize) very rapidly under the reaction conditions. Acid treatment of olefinic ketone **26** should surely give propionaldehyde from the initial reverse aldol reaction, but it could not be detected.

Reactions of olefinic ketones, having R_1 in general formula **4** an ethyl or a propyl group, yield simple rearranged ketones which cannot be explained by the above disproportionation mechanism. These reactions are summarized in Table III.

TABLE III

OLEFINIC KETONES GIVING SIMPLE KETONIC PRODUCTS
NOT PREDICTED BY THE DISPROPORTIONATION MECHANISM

Olefinic ketone	Simple ketonic products
EtMeC=CHCOEt *cis*- (**10**) and *trans*- (**11**)	Acetone
Et$_2$C=CMeCOEt (**18**)	Acetone
n-PrMeC=CHCO-*n*-Pr *cis*- (**19**) and *trans*- (**20**)	Butanone
Me$_2$C=CHCOEt (**22**)	Acetone
Me$_2$C=CHCO-*n*-Pr (**23**)	Butanone
MeCH=CMeCHEtCOEt (**24**)	Acetone
EtCH=CMeCOEt (**26**)	Acetone 2-Pentanone

All of the products obtained in these reactions are readily explainable on the basis of an oxygen function rearrangement[2,7] in the olefinic ketone, followed by a reverse aldol reaction. For instance, the reactions of **23** may be summarized as follows.
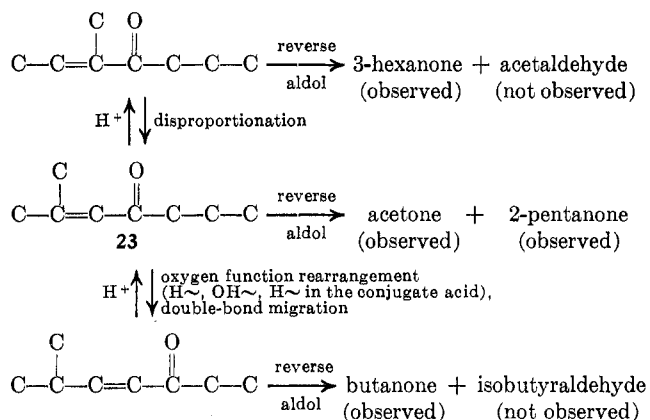
4-Methyl-4-hepten-3-one (**26**) gives acetone and 2-pentanone according to this mechanism. In fact the yield of 2-pentanone is 11.0% compared with 83.6% for the normal reverse aldol product, 3-pentanone, which shows that rearrangement of this compound by an oxygen migration is considerably more extensive than the disproportionation reaction.

Experimental Section

General Procedures for the Disproportionation Reaction.— Samples of the various ketones were stirred (or shaken) with 70% perchloric acid at appropriate temperature for various times. Typically, at 50°, the material became light yellow immediately after mixing and turned to a light brown after 24 hr and to a dark brown after 72 hr. The reaction mixtures were poured over cracked ice, and the solutions were neutralized with sodium hydroxide, saturated with sodium chloride, and extracted with ether. After removal of the ether, the remaining volatile material was collected by distillation. The components of the various fractions were analyzed by gas–liquid partition chromatography (glpc) on a variety of columns, and preparative glpc was used to isolate and purify compounds for spectral comparisons and derivative preparation in several instances.

A great many experiments were performed, involving variations in time from a few minutes to many days, in temperature from room temperature to 100°, and in ketone to acid ratio of from one to five. Recovery of volatile material was essentially quantitative for short-time, low-temperature experiments, and ranged downward to a few per cent (the rest being polymeric material) for high-temperature, long-time experiments. In many cases, the course of the reaction was followed by injection of a very small aliquot of the reacting mixture directly onto a glpc column. In the short-time, low-temperature experiments, barely detectable amounts of rearrangement products were formed. As conditions became more drastic, increasing ratios of rearranged to unrearranged products were found, but the amount of volatile material recovered decreased to only a few per cent.

A wide variety of analytical and preparative glpc columns of different polarity was used; frequently this resulted in a different order of elution on two columns for a series of ketones, thus facilitating positive identification. Gas chromatographs with both thermal conductivity and hydrogen flame detectors were used. A typical analysis consisted of injecting a glpc sample followed by (or preceded by) an authentic mixture of ketones under the same elution conditions. Retention times were then compared. Since the reaction product contained starting ketone, an internal standard was present which permitted the calculation of retention ratios and corrected for any minute change in conditions from one injection to another. In some cases, a small amount of known compound was added to the product and analyzed to provide further information. For the reactions of olefinic ketones, the reverse aldol reaction readily produces simple ketones as internal standards to permit the calculation of retention ratios. Details concerning many of the individual experi-

ments are contained in the Ph.D. dissertations of W. H. C.[8] and D. D. F.[9] Many of the nmr spectra and all of the mass spectra were taken by Dr. P. Flannigan and Mr. H. T. Ford of Continental Oil Co. We are deeply indebted to them for their assistance.

Experiments with Simple Ketones.—The results of the exploratory experiments with simple ketones are given in Table I. Positive identification of the disproportionation products and condensed olefinic ketones is vital to the research, and a typical glpc analysis of the material recovered from the reaction of butanone with 70% perchloric acid follows. For a 20% triethylene glycol on 60/80 firebrick column (100 ml/min He, 74°), retention times relative to butanone for the known compound and the reaction product mixture, respectively, follow: acetone, 0.71, 0.70; butanone, 1.00, 1.00; 2-pentanone, 1.44, 1.44; 3-pentanone, 1.36, 1.36; 3-hexanone, 1.81, 1.81. For a 200-ft capillary column of didecyl phthalate (5 ml/min He, 93°), the corresponding values follow: acetone, 0.88, 0.88; butanone, 1.00, 1.00; 2-pentanone, 1.22, 1.22; 3-pentanone, 1.24, 1.24; 3-hexanone, 1.68, 1.67. For a 20% Carbowax 4000 on 60/80 firebrick column (100 ml/min He, 94°), the values follow: acetone, 0.68, 0.67; butanone, 1.00, 1.00; 2- and 3-pentanone unresolved mixture, 1.47, 1.47 (the 3-hexanone peak was obscured by another product). For a 20% silicone gum rubber SE-30 on Celite column (100 ml/min He, 65°), the values follow: butanone, 1.00, 1.00; 2- and 3-pentanone unresolved mixture, 1.89 and 1.90 (the acetone and 3-hexanone peaks were obscured by other peaks). For the mixture of olefinic ketones formed, the relative steady-state concentrations, calculated from retention data on 1,2,3-tris(2-cyanoethoxy)propane, silicone gum rubber SE-30, and silicone fluid nitrile XF-1150 columns, was 4.1% unresolved **8** and **9**, 22.6% **10**, 67.1% unresolved **6** and **11**, and 6.2% **7**.

The 2- and 3-pentanone fraction from one experiment with butanone was recovered by preparative glpc and shown to be 10% 3-pentanone and 90% 2-pentanone by comparing its infrared spectra with that of an authentic sample. A 3-hexanone fraction was separated from a 3-pentanone reaction mixture by preparative glpc on a 20% triethylene glycol on 60/80 firebrick column, and identified by its infrared spectrum (neat) and the formation of a semicarbazone [mp 110–112° (lit.[10] mp 113°)] comparison with an authentic sample, mp 111–112°. Details of identification and derivative preparation for 2-pentanone formed from 3-pentanone are given elsewhere.[11]

In investigating the question of the formation of aldehydes from the disproportionation reaction, an experiment was carried out in a sweep system in an effort to remove the low-boiling aldehydes as quickly as they were formed. Butanone (10 g) was treated with 50 ml of 70% perchloric acid at 50° for 48 hr while being swept with 100 ml/min of dry nitrogen. After bubbling through the reaction mixture, the nitrogen was passed through a Dry Ice trap and then through sodium hydroxide bubblers. The liquid collected in the cold trap (mostly butanone) was analyzed by glpc and no acetaldehyde or propionaldehyde could be detected. No carbon dioxide (oxidation product) of hydrogen chloride (perchloric acid reduction product?) could be detected in the sodium hydroxide bubblers upon attempts to precipitate barium carbonate and silver chloride.

Exhaustive searches were carried out for branched-chain disproportionation products from straight-chain ketones, and for disproportionation products from α branched-chain ketones utilizing glpc analytical procedures similar to those described above.[8] As outlined in Table I, no such products were found. Detection limits of 0.05–1.0% relative to the recovered starting ketone were set. Control experiments demonstrated that the "expected" disproportionation products were sufficiently stable under the reaction conditions to be detected readily if they had been formed. In the course of these studies the reversibility of the intramolecular interconversion of 3-methyl-2-pentanone and 2-methyl-3-pentanone was established. The main products (ca. 50% actual yield) from the reaction of 3-methylbutanone with perchloric acid are two readily intercovertible compounds of molecular formula $C_{10}H_8O$. These compounds have not been identified as yet, but they are probably dihydrofurans. They are not C_{10} olefinic ketones.

Preparation, Isolation, and Identification of Olefinic Ketones and Dihydrofurans.—The preparation and characterization of compounds **6**, **7**, **10**, **11**, **18–23**, **25**, and **26** are described elsewhere.[12]

4-Ethyl-5-methyl-5-hepten-3-one (24).[13]—Ethyl 2-ethyl-3-hydroxy-3-methylpentanoate (**35**), bp 85–87° (10 mm), was prepared in 81% yield by dropwise addition at reflux of an ether solution of 46 g (0.65 mol) of butanone and 100 g (0.51 mol) of ethyl α-bromobutyrate to 13 g of magnesium and 1.0 g of mercuric chloride.

Data for **35** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.88 (t, 6 H, CH_2CH_3), 1.09 (s, 3 H, CCH_3), 1.28 (t, 3 H, OCH_2CH_3), ca. 1.47 (m, 4 H, CCH_2CH_3 and $CHCH_2CH_3$), 2.15 (t, 1 H, $CHCH_2$), 2.62 (s, broad, 1 H, OH), and 4.16 (q, 2 H, OCH_2CH_3); ir (neat) ν_{max}^{NaCl} 3480 (m, broad, OH), 1715 (s, C=O), and 1188 cm⁻¹ (s, ester COC stretching frequency).

Hydroxy ester **35** was dehydrated by refluxing for 20 min with iodine in a water separator to give an 87% yield of ethyl 2-ethyl-3-methyl-3-pentenoate, bp 66.5–71° (10 mm). The olefinic ester was hydrolyzed in aqueous alcoholic sodium hydroxide to give a 92% yield of 2-ethyl-3-methyl-3-pentenoic acid (**36**), bp 104–110° (10 mm). The nmr spectrum indicated the presence of a cis–trans mixture.

Data for **36** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.87 (t, 3 H, CH_2CH_3), 1.64 (s, fine splitting, 3 H, CH=CCH₃), 1.65 (d, 3 H, CH₃CH=C), 1.70 (m, partially obscured, 2 H, CHCH₂CH₃), 2.82 (t, <1 H, α H of the geometric isomer having the γ H and the carboxyl group cis), 3.38 (t, <1 H, α H of the geometric isomer having the γ H and the carboxyl group trans), 4.97 (q, broad, <1 H, γ H trans to the carboxyl group), 5.41 (q, broad, <1 H, γ H cis to the carboxyl group), and 11.22 (s, 1, H, OH); ir (neat) ν_{max}^{NaCl} 2950 (s, broad, OH), 1700 (s, carboxylic acid dimer C=O), 1411 (m, dimeric OH in-plane bending frequency coupled with CO stretching frequency), 1220 (s, CO stretching frequency coupled with OH in-plane bending frequency), 932 (m, broad, OH out-of-plane bending frequency of an acid dimer), and 812 cm⁻¹ (m, CH bending frequency of a trisubstituted double bond).

Thionyl chloride was dried dropwise to the acid **36** at 70°, giving a 90% yield of 2-ethyl-3-methyl-3-pentenoyl chloride (**37**), bp 56–64° (10 mm).

Data for **37** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.88 (t, 3 H, CH_2CH_3), 1.63 (d, 3 H, C=CHCH₃), 1.65 (s, fine splitting, 3 H, CH=CCH₃), ca. 1.70 (m, partially obscured, 2 H, CHCH₂CH₃), 2.81 (t, 1 H, CH_2CH), and 5.40 (q, broad, 1 H, CH₃CH=CCH₃); ir (neat) ν_{max}^{NaCl} 1795 cm⁻¹ (s, acid chloride C=O).

Acid chloride **37** in benzene solution was added to a benzene solution of diethylcadmium to give an 81% yield of 4-ethyl-5-methyl-5-hepten-3-one (**24**), bp 58.5–59.5° (10 mm).

Data for **24** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.78 (t, 3 H, CHCH₂CH₃), 0.98 (t, 3 H, COCH₂CH₃), 1.48 (s, fine splitting, 3 H, CH=CCH₃), 1.63 (d, fine splitting, 3 H, CH₃C=CHCH₃), 1.64 (quintet, partially obscured, 2 H, CHCH₂CH₃), 2.32 and 2.40 (pair of quartets, 2 H, COCH₂CH₃), 2.87 (t, <1 H, α H of the geometric isomer having the γ H cis to the carbonyl group), 3.41 (t, <1 H, α H of the geometric isomer having the γ H trans to the carbonyl group), and 5.40 (q, 1 H, CH₃CH=C); ir (neat) ν_{max}^{NaCl} 3016 (w, vinyl H), 1712 (s, C=O), and 808 cm⁻¹ (m, CH bending frequency of a trisubstituted double bond); uv λ_{max}^{EtOH} 291 mμ (log ε 2.65); mass spectrum m/e (rel intensity) 154 (parent peak) (1.7), 125 (29), 97 (44), 69 (28), 57 (80), 55 (100), 43 (11), 41 (31), 39 (19), 29 (62), and 27 (34).

cis- (12) and trans-2,3,4,5-Tetramethyl-4,5-dihydrofuran (13).—The main nonpolymeric products from the reaction of butanone with 70% perchloric acid are **12** and **13**. This may be the method of choice for the preparation of compounds of this type. In an experiment with 1 g of butanone per 5 ml of 70% perchloric acid at 95° for 4 hr, the yield of a mixture of **12** and **13** was 21% (56% of the butanone weight was recovered as high-boiling polymeric material). In butanone–perchloric acid experiments under mild conditions (low temperature, short time), the **12** to **13** ratio was ca. four, and this decreased to less than one for high-temperature, long-time experiments. It appears that **12** is formed faster than **13** but **13** is more stable than **12**, although precise rate and equilibration studies were not carried out. Further details concerning yields, relative yields, etc., are found in the Ph.D. thesis of D. D. F.[9] We are indebted to Dr. P. Flannigan and Mr. H. T. Ford of Continental Oil Co. for assistance in

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TABLE IV

RELATIVE YIELDS OF SIMPLE KETONES IN REACTIONS OF OLEFINIC KETONES WITH PERCHLORIC ACID

Compd	Ml of HClO₄/g of ketone	Time, hr	Temp, °C	Relative yields, %				
				MeCOMe	EtCOMe	EtCOEt	n-PrCOMe	n-PrCOEt
Me₂C=CHCOMe (5)	3.0	100.00	25	98.6ᵃ	1.4	...	...	...
EtMeC=CMeCOMe (6 and 7)	5.0	1.0	50	...	99.6ᵃ	...	0.4	...
EtMeC=CMeCOMe (6 and 7)	0.02	0.017	25	1.9	91.4ᵃ	...	6.7	...
EtMeC=CHCOEt (10 and 11)	3.0	634.0	0	0.3	96.6ᵃ	3.1	...	...
EtMeC=CHCOEt (10 and 11)	3.0	3.0	50	0.1	91.6ᵃ	8.3	...	...
Et₂C=CMeCOEt (18)	3.3	8.0	50	...	0.9	99.1ᵃ	...	...
Et₂C=CMeCOEt (18)	2.0	0.017	25	2.1	1.1	94.0ᵃ	...	2.8
n-PrMeC=CHCO-n-Pr (19 and 20)	5.0	2.5	50	...	0.6	...	99.4ᵃ	Trace
Me₂C=CEtCOMe (21)	5.0	0.5	50	24.5ᵃ	1.9	...	73.6ᵃ	...
Me₂C=CHCOEt (22)	5.0	24.0	25	...	99.7ᵃ	0.3	Trace	...
MeC=CMeCHEtCOEt (24)	3.0	1.5	20	...	...	0.4	...	99.6ᵃ
MeCH=CMeCOMe (25)	6.0	1.0	50	12.0	88.0ᵃ	...	...	...
EtCH=CMeCOEt (26)	5.0	10.0	25	1.9	1.8	83.6ᵃ	11.0	1.7

ᵃ Unrearranged reverse aldol product; other values are for rearranged products.

the interpretation of the nmr and mass spectra of these and other dihydrofurans.

Data for **12** follow: bp 137–138°; d^{24} 0.870 g/ml; n^{25}D 1.439; nmr $\delta_{CCl_4}^{TMS}$ 0.86 (d, 3 H, OCCHCH₃), 1.17 (d, 3 H, OCHCH₃), 1.52 [s, fine splitting, 3 H, OC(CH₃)=CCH₃], 1.60 [s, fine splitting, 3 H, OC(CH₃)=CCH₃], 2.53 (broad quintet, 1 H, OCH-CHCH₃), and 4.32 and 4.48 [pair of quartets, 1 H, OCH-(CH₃)CH, $J_{OCHCHCH_3}$ = 8.6 Hz]; ir (neat) ν_{max}^{NaCl} 1708 (s, C=C), 1214 (s, asymmetric stretching frequency of =COC), 1063 (m, symmetric stretching frequency of =COC), and 908 cm⁻¹ (m, ring bending frequency); uv λ_{max}^{EtOH} end absorption; mass spectrum m/e (rel intensity) 126 (parent peak) (19), 111 (66), 83 (16), 67 (23), 56 (6), 55 (41), 53 (11), 43 (100), 41 (36), 39 (26), 29 (16), 28 (10), 27 (30), and 15 (23); positive potassium permanganate double bond test.

Data for **13** follow: bp 128–129°; n^{25}D 1.438; nmr $\delta_{CCl_4}^{TMS}$ 0.98 (d, 3 H, OCCHCH₃), 1.22 (d, 3 H, OCHCH₃), 1.48 [s, fine splitting, 3 H, OC(CH₃)=CCH₃], 1.61 [s, fine splitting, 3 H, OC-(CH₃)=CCH₃], 2.28 (broad quintet, 1 H, OCHCHCH₃), and 3.79 and 3.90 [pair of quartets, 1 H, OCH(CH₃)CH, $J_{OCHCHCH_3}$ = 7.6 Hz]; ir (neat) ν_{max}^{NaCl} 1711 (s, C=C), 1202 (s, asymmetric stretching frequency of =COC), 1060 (m, symmetric stretching frequency of =COC), and 910 (m, ring-bending frequency); uv λ_{max}^{EtOH} end absorption; mass spectrum m/e (rel intensity) 126 (parent peak) (19), 111 (75), 83 (12), 67 (19), 56 (12), 55 (39), 53 (11), 43 (100), 41 (36), 39 (27), 29 (16), 28 (18), 27 (31), and 15 (23); positive potassium permanganate double bond test.

cis- (**16**) and *trans-*2,4-Diethyl-3,5-dimethyl-4,5-dihydrofuran (**17**).—The main nonpolymeric products from the reaction of 3-pentanone with 70% perchloric acid are **16** and **17**. These compounds are also major products in the reaction of 5-ethyl-4-methyl-5-hepten-3-one (**14** and **15**) with perchloric acid. Pure samples were prepared by preparative glpc using a 0.375 in. × 10 ft 30% Carbowax 4000 on 60/80 firebrick column. Further details concerning these compounds are found in the Ph.D. thesis of W. H. C.[8]

Data for **16** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.80–2.02 (overlapping complex, 13 H, CHCH₂CH₃, C=CCH₂CH₃, and OCHCH₃), 1.53 (s, 3 H, C=CCH₃), 2.39 [m, 1 H, C=CCH(CH₂-)CH], and 3.90 and 4.41 [pair of quartets, 1 H, OCH(CH₃)CH]; ir (neat) ν_{max}^{NaCl} 1701 cm⁻¹ (s, C=C); mass spectrum m/e (rel intensity) 154 (parent peak) (20), 125 (100), 69 (20), 67 (11), 57 (21), 55 (37), 53 (11), 43 (86), 41 (36), 39 (21), 29 (44), and 27 (32).

Data for **17** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.83–1.49 (overlapping complex, 11 H, CHCH₂CH₃, C=CCH₂CH₃, and OCHCH₃), 1.49 (s, 3 H, C=CCH₃), *ca.* 2.02 [overlapping quartets, 3 H, CH₃CH₂=C and C=CCH(CH₂-)CH], and 4.01 [quintet, 1 H, OCH(CH₃)-CH]; ir (neat) ν_{max}^{NaCl} 1705 cm⁻¹ (s, C=C); mass spectrum m/e (rel intensity) 154 (parent peak) (19), 125 (100), 69 (13), 57 (17), 55 (31), 43 (83), 41 (31), 39 (18), 29 (40), and 27 (28).

cis- (**31**) and *trans-*2,3-Diethyl-4,5-dimethyl-4,5-dihydrofuran (**32**).—A mixture of compounds **31** and **32**, bp 55–84° (mainly 76.5–79°) (10 mm), was formed in 63% yield upon treatment of 4-ethyl-5-methyl-5-hepten-3-one (**24**) with 70% perchloric acid at 30° for 1.5 hr. Pure samples of **31** and **32** were separated by preparative glpc on a 0.375 in. × 12 ft 30% Carbowax 4000 on 60/80 firebrick column.

Data for **31** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.85 (d, 3 H, CCHCH₃), 0.94 (t, 3 H, OC=CCH₂CH₃), 0.98 (t, 3 H, OCCH₂CH₃), 1.17 (d, 3 H, OCHCH₃) 1.98 (q, 2 H, OC=CCH₂CH₃), 2.00 (q, 2 H, OCCH₂CH₃), 2.68 (broad quintet, 1 H, OCHCHCH₃), and 4.27 and 4.41 [pair of quartets, 1 H, OCH(CH₃)CH, $J_{OCHCHCH_3}$ = 8.80 Hz]; ir (neat) ν_{max}^{NaCl} 1891 (m, C=C), 1208 (m, asymmetric stretching frequency of =COC), 1040 (m, symmetric stretching frequency of =COC), and 880 (m, ring bending frequency); uv λ_{max}^{EtOH} end absorption; mass spectrum m/e (rel intensity) 154 (parent peak) (26), 140 (11), 139 (100), 137 (10), 111 (14), 97 (12), 95 (10), 83 (11), 81 (15), 69 (36), 67 (11), 57 (77), 56 (10), 55 (47), 53 (16), 43 (60), 41 (46), 39 (29), 29 (61), 28 (19), 27 (42), 18 (35), and 15 (15).

Data for **32** follow: nmr $\delta_{CCl_4}^{TMS}$ 0.93 (t, 3 H, OC=CCH₂CH₃), 0.96 (d, 3 H, CCHCH₃), 0.97 (t, 3, H, OCCH₂CH₃), 1.20 (d, 3 H, OCHCH₃), 1.95 (q, 2 H, OC=CCH₂CH₃), 2.01 (q 2 H, OCCH₂CH₃), 2.41 (broad quintet, 1 H, OCHCHCH₃), and 3.76 and 3.87 [pair of quartets, 1 H, OCH(CH₃)CH, $J_{OCHCHCH_3}$ = 6.7 Hz]; ir (neat) ν_{max}^{NaCl} 1887 (m, C=C), 1197 (m, asymmetric stretching frequency of =COC), 1027 (s, symmetric stretching frequency of =COC), and 890 (m, ring bending frequency); uv λ_{max}^{EtOH} end absorption; mass spectrum m/e (rel intensity) 154 (parent peak) (23), 140 (14), 139 (100), 137 (31), 111 (18), 97 (24), 95 (11), 83 (16), 81 (13), 69 (42), 67 (15), 57 (90), 56 (16), 55 (55), 53 (19), 43 (93), 41 (63), 39 (37), 29 (76), 28 (26), 27 (55), 18 (23), and 15 (20).

Reactions of Olefinic Ketones with Perchloric Acid.—Olefinic ketones were treated with perchloric acid and the products were analyzed utilizing the procedures described above. In some cases, several reactions were performed with a particular olefinic ketone so that the optimum conditions for the rearrangement reaction could be determined. In other cases, the supply of olefinic ketone permitted only one reaction. Since the optimum conditions are not the same for all olefinic ketones, it was necessary to use past experience to choose the reaction conditions. It was desirable to choose conditions which permitted significant recovery of starting olefinic ketone so that a comparison could be made between the simple reverse aldol reaction and the reverse aldol reaction of the rearranged olefinic ketone. The main products from the reactions of most olefinic ketones with perchloric acid appear to be dihydrofuran derivatives which are formed at rates depending on structure, *i.e.*, highly branched olefinic ketones form dihydrofurans at a faster rate. Therefore, to prevent gross conversion into dihydrofuran derivatives, highly branched olefinic ketones were reacted in relatively low acid concentration and/or at relatively low temperatures. Representative results of these experiments are given in Table IV. The relative yield values given for the simple aliphatic ketones are for the products from that part of the reaction going through the reverse aldol reaction.

From Table IV, it is seen that mesityl oxide (**5**) gives *ca.* 2.8% rearrangement [(100 × % butanone × 2)/% acetone] for the 100-hr reaction at 25°, since the rearrangement reaction gives one molecule of butanone and one molecule of acetaldehyde, while the reverse aldol reaction gives two molecules of acetone. [This assumes that acetone and butanone are consumed in other (polymerization) reactions at the same rate after they are formed.]

Similarly, the reaction of a mixture of the geometric isomers of 5-methyl-4-hepten-3-one (10 and 11) at 50° for 3.0 hr indicates 17.8% [100 (8.3 × 2)/91.6] rearrangement for that part of the reactants going through the reverse aldol reaction. However, in this case, the actual yield of butanone and 3-pentanone is low and the starting material is almost completely reacted. In this reaction, acetone cannot conceivably be produced *via* the proposed disproportionation mechanism; it is probably formed *via* an oxygen function migration in the olefinic ketone prior to dealdolization (see Discussion).

In the reaction of 18 with perchloric acid, the dihydrofuran fraction was also isolated and analyzed. It consisted of 95.8% unrearranged *cis* and *trans* dihydrofurans 16 and 17, and 3.5% of 31 plus 0.7% of 32, the *cis* and *trans* rearranged dihydrofurans. Dihydrofurans are relatively stable in perchloric acid, so this 4.2% rearrangement is probably a good measure of relative rates of rearrangement and dihydrofuran formation.

Rearranged dihydrofurans 12 and 13 were also detected in the reaction of 21 with perchloric acid.

It is interesting to note that 21 produces a significantly higher ratio of 2-pentanone to acetone than the 1:1 mixture expected from the reverse aldol reaction. Based on this fact and general observations about the reactivity of various ketones, it appears that lower molecular weight ketones disappear (polymerize) faster in perchloric acid than their higher molecular weight homologs. For this reason the relative yields in Table IV are highly dependent on reaction conditions.

Mass Spectrometry in Structural and Stereochemical Problems. CLXXXI.[1] Further Studies of Remote Group Interactions after Electron Impact in 4-Substituted Cyclohexanones[2]

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The mass spectral properties of a series of 4-substituted cyclohexanones have been investigated in an attempt to determine the scope and limitation of an electron impact induced oxygen rearrangement previously reported in the 4-hydroxy and 4-methoxy analogs. With the use of deuterium labeling, a similar rearrangement has been elucidated for 4-ethoxycyclohexanone, albeit to a smaller extent than in the methoxy analog. The mass spectral decomposition of 4-benzyloxycyclohexanone results in another important rearrangement process, giving styrene and a γ,δ-unsaturated acid as the final products, both of which retain part of the ionizing current. For several other analogs, including some containing a different oxygenated substituent, and others bearing a heteroatom (chlorine, sulfur) other than oxygen at the 4 position, no rearrangement processes are observed. Instead, the major fragmentation pathways are governed by the position of initial ionization, as determined by the relative ionization potentials of the different substituent groups.

The use of mass spectrometry in the structure elucidation of organic molecules is now widely accepted, and the characteristic fragmentation patterns associated with individual functional groups have been well documented.[4] Although the techniques of high-resolution analysis, isotopic labeling, and metastable analysis have assisted the chemist greatly in the structure determination of fragment ions, erroneous conclusions are still possible if a fragmentation pathway involves a molecular rearrangement process.

Until recently most reported electron impact induced rearrangements have involved transfer of a hydrogen atom or a simple alkyl radical,[4,5] usually producing a more stable fragment ion. Recent work, however, has uncovered rearrangements of larger groups.[5] For example, during the course of a systematic study of bifunctionalized monocyclic systems in this laboratory, it was reported[6] that abundant

fragment ions of masses 60 and 74, respectively, occurred in the mass spectra of 4-hydroxycyclohexanone (I) and 4-methoxycyclohexanone (II). From the elemental composition of these ions ($C_2H_4O_2$ and $C_3H_6O_2$, respectively) it followed that they were produced through a rearrangement process, bringing the two oxygen functions closer together in the daughter than they were in the parent ion. With the use of extensive deuterium labeling the rearrangement mechanism was deduced to be as in Scheme I.

In addition to the oxygen rearrangement summarized in Scheme I, other fragmentation pathways containing rearrangements of heteroatoms have been reported in the mass spectra of such compounds as methylglycosides,[7] β-(alkylthio)propionic acids and esters,[8a] dimethyl esters,[8b] and 1,4-naphthoquinone dimers.[8c] Also, we have recently found that a rearrangement, similar to that reported by Green and Djerassi, occurs in the corresponding α-decalone series,[1] except that in this system charge retention occurred on the more highly substituted hydrocarbon, rather than the oxygen-containing portion of the molecule.

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