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EVIDENCE FOR A PROTONATED CYCLOPROPANE INTERMEDIATE IN THE SULFURIC ACID-CATALYZED DEHYDRATION-REARRANGEMENT OF 2,2-DIMETHYL-1,3-PROPANEDIOL.

City University of New York, Ph.D., 1977
Chemistry, organic

# EVIDENCE FOR A PROTONATED CYCLOPROPANE INTERMEDIATE IN THE SULFURIC ACID-CATALYZED DEHYDRATION-REARRANGEMENT OF 2,2-DIMETHYL-1,3-PROPANEDIOL

by

Lawrence Fred Leibman

1977

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

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## Abstract

The purpose of this research was to investigate recently discovered pathways in the sulfuric acid-catalyzed rearrangement of 2,2-dimethyl-1,3-propanediol to 3-methyl-2-butanone.

The reaction of 2,2-dimethyl-1,3-propanediol-$(OD)_2$ with 55% deuteriosulfuric acid at 150° gave 3-methyl-2-butanone which was 68.1% deuterated. Mass spectral evidence indicated that 39%±1% of the ketone was completely deuterated ($d_{10}$ species). Completely deuterated 3-methyl-2-butanone was attributed to pathways which include 1-methylcyclopropylcarbinol as an intermediate.

When 2,2-(dimethyl-$^{14}C$)-1,3-propanediol was allowed to react with 55% sulfuric acid at 150°, the 3-methyl-2-butanone product was found to have carbon-14 label distributed among all of its carbon atoms. The carbon-14 distribution pattern was consistent with 27%±5% of 3-methyl-2-butanone being formed through pathways which include 1-methylcyclopropylcarbinol as an intermediate.

Dedication

To Shelley

Acknowledgements

I wish to express appreciation to Dr. Leonard H. Schwartz for his guidance of this research.

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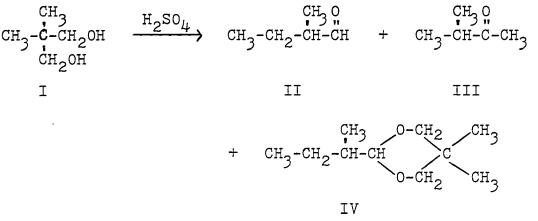
## Background

The sulfuric acid-catalyzed dehydration-rearrangement of 2,2-dimethyl-1,3-propanediol (I) was reported as early as 1900.[1] It was not until 1961, however, that Gladstone[2] first reported the correct products to be 2-methylbutanal (II), 3-methyl-2-butanone (III) and 5,5-dimethyl-2-(2-butyl)-1,3-dioxane (IV) (incorrectly reported as 2,2-dimethyl-2-(2-butyl)-1,3-dioxane).



I II III IV

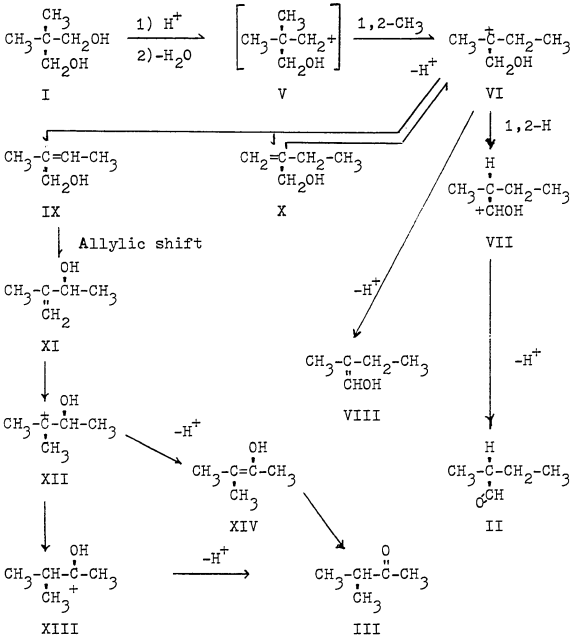
Yvernault and Mazet[3,4,5,6] later confirmed these products and carried out extensive investigations of the sulfuric acid-catalyzed dehydration-rearrangement of various 2,2-disubstituted 1,3-propanediols. The effects of different acid concentrations and reaction temperatures on product composition were studied.[4] Sixteen symmetrical and non-symmetrical 2,2-disubstituted 1,3-propanediols[5,6] were reacted with sulfuric acid to study the migration aptitudes of the substituent groups. Yvernault and Mazet interpreted all of their results in terms of the same mechanistic pathway proposed by

Gladstone,[2] which was based, in part, on the work of Green and Hickinbottom.[7] This pathway is represented by Mechanism I, p. 3.

Mechanism I involves the loss of water from protonated diol I and a 1,2-methyl shift to form tertiary cation VI. Primary carbonium ions, such as V, are bracketed and probably do not have any separate existence. Cation VI could undergo a 1,2-hydride shift to the more stable protonated aldehyde VII, which would deprotonate to give 2-methylbutanal (II). The charge in cation VI could also be dissipated by the direct elimination of a proton in three different directions to form unsaturated compounds VIII, IX or X. Compound VIII is the enol form of aldehyde II. 2-Methyl-2-buten-1-ol (IX) could undergo an allylic rearrangement to 3-methyl-3-buten-2-ol (XI). Protonation of XI would lead to XII, which like VI, could undergo a 1,2-hydride shift to form a protonated carbonyl compound, XIII, which could deprotonate to 3-methyl-2-butanone (III). Cation XII could also form III through its enol, XIV. 2-Ethyl-2-propen-1-ol (X) could also undergo an allylic rearrangement, but it would be unproductive since it would not lead to a new species. 5,5-Dimethyl-2-(2-butyl)-1,3-dioxane (IV) results from the condensation of II with the starting diol, I.

Green and Hickinbottom[7] reported that, upon reaction with sulfuric acid, X gives aldehyde II; XI gives ketone III and IX gives a mixture of both II and III in a 1:2.5 ratio This work[7] was cited by both Gladstone[2] and Yvernault and

Mechanism I: Formation of 2-Methylbutanal (II) and 3-Methyl-2-butanone (III) through the Allylic Shift Pathway[a] in the Sulfuric Acid-Catalyzed Dehydration-Rearrangement of 2,2-Dimethyl-1,3-propanediol (I).




[a]Essentially the mechanism proposed by Gladstone[2] and Yvernault and Mazet.[3]

Mazet[3,4] in the formulation of Mechanism I, p. 3.

Demerseman and Royer[8] reported II, III and IV to be the main products of the reaction of I with pyridinium hydrobromide. They cited the work of Yvernault and Mazet[3] and described the products as forming through intermediates VI and IX of mechanism I.

For simplicity in further mechanisms in this thesis, it will be assumed that, in Mechanism I, p. 3, aldehyde II forms through VII and that ketone III forms through XIII. There are no mechanistic consequences of this assumption.

Kascheras[9] reacted diol I with 50% deuteriosulfuric acid ($D_2SO_4$) and determined the deuterium incorporation in the volatile products. 2-Methylbutanal (II) was 13.3% deuterated and consisted mainly of $d_1$ and $d_2$ species (Table I, p. 5). 3-Methyl-2-butanone (III) was 65.0% deuterated, and the major deuterated species were $d_5$, $d_6$, $d_7$ and $d_{10}$ (Table II, p. 6).

The formation of mono- and dideuterated aldehyde II is compatible with the allylic shift pathway (Mechanism II, p. 7), provided that the formation of aldehyde II from cation VI is reversible (see Scheme I, p. 8) and that the α-hydrogens of II are exchangeable. According to Scheme I, aldehyde II is progressively deuterated by a series of α-exchanges and 1,2-deuteride and 1,2-hydride shifts. Such 1,2-shifts in protonated aldehydes have been previously reported.[10] When aldehyde II was reacted with 50% $D_2SO_4$[9] the recovered II consisted mostly of the $d_2$ species (Table I,

Table I: Percent Deuterium Incorporation and Isotopic Distribution in 2-Methylbutanal (II) from Reactions in 50% $D_2SO_4$.[a]

| | | Isotopic Distribution m/e%[b] | | | | | |
|---|---|---|---|---|---|---|---|
| | Percent | 86 | 87 | 88 | 89 | 90 | 91 |
| Reactant | Incorporation | $d_0$ | $d_1$ | $d_2$ | $d_3$ | $d_4$ | $d_5$ |
| I | 13.3 | 15.5 | 45.8 | 30.8 | 6.0 | 1.9 | 0.0 |
| II | 16.8 | 12.4 | 28.7 | 51.5 | 6.9 | 0.8 | 0.0 |

[a]Taken from reference 9, p. 14.

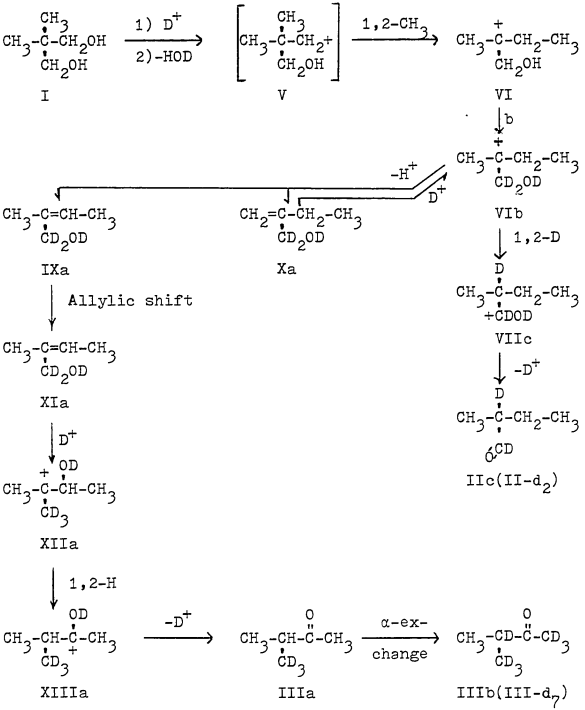
[b]Corrected for (M+1) contribution, but not for (M-1) contribution which is 4.1% M in unlabeled 2-methylbutanal (II).

Table II: Percent Deuterium Incorporation and Isotopic Distribution in 3-Methyl-2-butanone (III) from Reactions in 50% $D_2SO_4$.[a]

| | Reactant | % Deuterium Incorporation | Isotopic Distribution m/e%[b] 86 ($d_0$) | 87 ($d_1$) | 88 ($d_2$) | 89 ($d_3$) | 90 ($d_4$) | 91 ($d_5$) | 92 ($d_6$) | 93 ($d_7$) | 94 ($d_8$) | 95 ($d_9$) | 96 ($d_{10}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $(CH_3)_2C(CH_2OH)_2$ | 65.0 | 0.8 | 0.3 | 0.5 | 0.6 | 5.2 | 32.4 | 19.1 | 16.3 | 3.7 | 3.9 | 16.8 |
| II | $CH_3-\overset{CH_3O}{\overset{\vert}{C}}H-\overset{O}{\overset{\Vert}{C}}-CH$ | 70.9 | 0.9 | 1.7 | 2.3 | 1.3 | 2.9 | 5.9 | 20.6 | 31.2 | 6.4 | 7.8 | 18.5 |
| III | $CH_3-\overset{CH_3O}{\overset{\vert}{C}}H-\overset{O}{\overset{\Vert}{C}}-CH_3$ | 38.9 | 0.7 | 1.4 | 2.1 | 4.7 | 90.3 | 0.0 | 0.1 | 0.7 | 0.0 | 0.0 | 0.0 |
| IX | $CH_3-C(CH_2OH)=CH(OH)-CH_3$ | 51.9 | 1.3 | 1.4 | 1.2 | 1.2 | 6.7 | 74.5 | 3.5 | 2.5 | 1.2 | 1.1 | 5.4 |
| XI | $CH_2=C(CH_2OH)-CH_2-CH_3$ | 50.6 | 1.0 | 1.2 | 0.9 | 1.2 | 8.1 | 78.0 | 3.1 | 1.5 | 0.8 | 0.8 | 3.4 |
| XVIII |  | 95.5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.3 | 0.9 | 2.7 | 8.5 | 24.5 | 63.0 |
| XLIV | $HOCH_2-\overset{CH_3}{\overset{\vert}{C}}(OH)-CH_2-CH_3$ | 64.3 | 0.1 | 0.8 | 1.1 | 1.6 | 5.6 | 29.4 | 16.2 | 23.8 | 4.4 | 3.2 | 13.8 |
| XLIX | $CH_2=\overset{CH_3}{\overset{\vert}{C}}-CH_2-CH_2OH$ | 93.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.2 | 0.7 | 2.7 | 4.9 | 9.4 | 20.6 | 61.5 |

[a]Taken from reference 9, p. 18. [b]Corrected for (M+1) contribution.

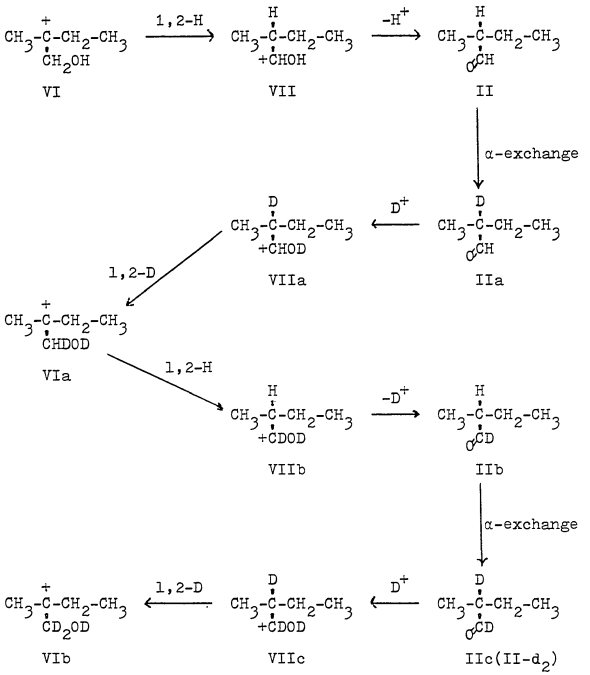
Mechanism II: Formation of 2-Methylbutanal (II-$d_2$) and 3-Methyl-2-butanone (III-$d_7$) through the Allylic Shift Pathway[a] in the $D_2SO_4$-Catalyzed Dehydration-Rearrangement of 2,2-Dimethyl-1,3-propanediol (I).




[a]See footnote Mechanism I, p. 3.

[b]See Scheme I, p. 8.

Scheme I: Formation of 2-Methylbutanal ($II-d_2$) and VIb from Intermediate VI.[a]




[a]See Mechanism II, p. 7.

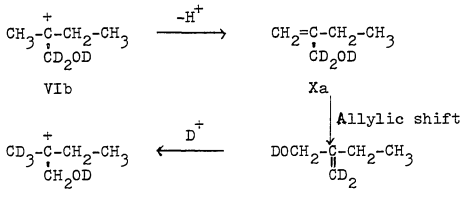
p. 5). This is evidence for the formation of II from VI (Mechanism II, p. 7) through Scheme I, p. 8.

When ketone III was reacted with 50% $D_2SO_4$[9] recovered III consisted of predominantly the $d_4$ species (Table II, p. 6), demonstrating both the exchangeability of its α-hydrogens and its resistance to further deuteration. Step XIa → XIIa of Mechanism II, p. 7 predicts the incorporation of one deuterium atom into III, and the reaction steps shown in Scheme I, p. 8, could account for the incorporation of one or two more. These two paths together with α-exchange could account for the formation of ketone III containing $d_5$, $d_6$ and $d_7$ species.

It is the deuterium incorporation beyond $d_7$ in III that is of most interest. The $d_8$ and $d_9$ contributions are minor while that of $d_{10}$ is major (Table II, p. 6). Mechanism II, p. 7, can accomodate the incorporation of more than seven deuterium atoms in two manners. One involves the allylic rearrangement of Xa → Xb (Scheme II, p. 10) followed by the reversal of VI → X, i.e., Xb → VIc and the other involves the reversal of XIa → XIIa (Scheme III, p. 10).

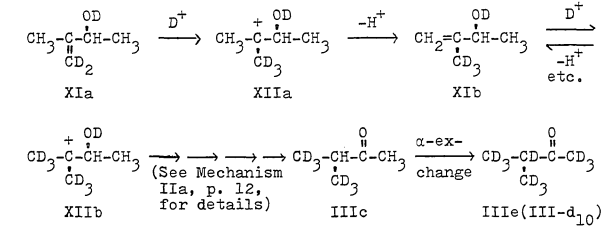
In Scheme II, p. 10, an allylic rearrangement of Xa → Xb would interchange the methylene deuteriums of the hydroxymethyl group with the vinyl hydrogens. Deuteration of Xb would lead to VIc. In VIc the methylene hydrogens of the hydroxymethyl group are available for deuterium exchange through Scheme Ia, p. 11, to form VIe and VIf. Intermediates VIc, VIe and VIf could account for the formation of aldehyde II-($d_3$-$d_5$) and

Scheme II: Allylic Rearrangement of Xa → Xb and Reversal of VI → X in Mechanism II.

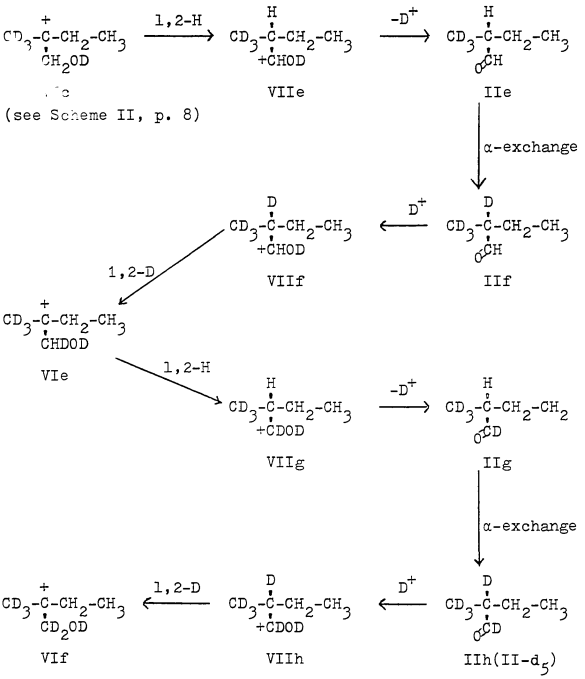



ketone III-($d_8$-$d_{10}$) through the allylic shift pathway (see i.e., Mechanism IIa, p. 12). The paucity of deuterated aldehyde containing more than two deuterium atoms (Table I, p. 5), however, is evidence that Scheme II does not play the major role in the formation of either aldehyde II or ketone III.

Scheme III: Formation of 3-Methyl-2-butanone (III-$d_{10}$) through the Reversal of 3-Methyl-3-buten-1-ol-(OD) (XIa) → Cation XIIa in Mechanism II.

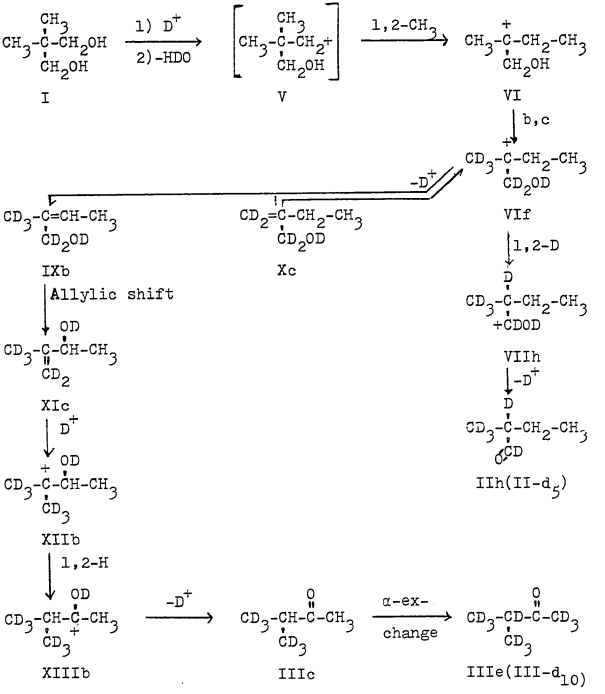


Scheme Ia: Formation of 2-Methylbutanal (II-$d_5$) and VIf from Intermediate VIc.[a]




[a]See Scheme I, p. 8.

Mechanism IIa: Formation of 2-Methylbutanal (II-$d_5$) and 3-Methyl-2-butanone (III-$d_{10}$) through the Allylic Shift Pathway[a] in the $D_2SO_4$-Catalyzed Dehydration-Rearrangement of 2,2-Dimethyl-1,3-propanediol (I).




I, V, VI, VIf, IXb, Xc, XIc, XIIb, XIIIb, VIIh, IIh(II-$d_5$), IIIc, IIIe(III-$d_{10}$)

[a] See footnote, Mechanism I, p. 3.

[b] See Scheme II, p. 10.

[c] See Scheme Ia, p. 11.

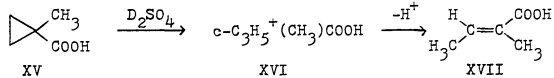
Repeated deuterium exchange in deuteriosulfuric acid between the XI and XII species of Scheme III, p. 10, would eventually lead to XIIb and, in turn, IIIc (see Mechanism IIa, p. 12). Upon α-exchange, IIIc could give fully deuterated ketone III-$d_{10}$. When allylic alcohol XI was reacted with 50% $D_2SO_4$,[9] the ketone III product consisted mainly of a $d_5$ species and only a minor amount of $d_{10}$ species (Table II, p. 6). This finding is consistent with the irreversibility of XIa → XIIa in Mechanism II, p. 7.

The labeling pattern in aldehyde II of $d_3 > d_4 > d_5$ (Table I, p. 5), and the total contribution of these species, is consistent with, at most, a minor contribution from the reactions of Scheme II, p. 10, and/or Scheme III, p. 10, to Mechanism II, p. 7. The labeling pattern in ketone III of $d_8$, $d_9 \ll d_{10}$ (Table II, p. 6), however, suggests a totally different mechanism, not part of Mechanism II, p. 7.

The presence of a substantial quantity of III-$d_{10}$, therefore, precludes Mechanism II, p. 7, as the sole source of 3-methyl-2-butanone (III) from diol Ia. Moreover, the labeling pattern in III of a minimum at $d_8$ and $d_9$ (Table II, p. 6) suggests the simultaneous operation of at least two mechanisms, one leading to III-($d_5$-$d_7$) (Mechanism II, p. 7), and (at least) one other leading to mainly III-$d_{10}$.

Protonated cyclopropanes are intermediates in the addition of acids to cyclopropanes[11,12] and account for some of the hydrogen scrambling in the 2-butyl cation.[13] Deno[14] has suggested that a protonated cyclopropane intermediate (XVI)

might account for the multiple deuteration (1.84 deuterium atoms per molecule) and deuterium scrambling (1.5 deuterium atoms in the methyl groups and 0.34 in C-3) found in the




XV XVI XVII

trans-2-methyl-2-butenoic acid (XVII) product of the ring opening of 1-methylcyclopropylcarboxylic acid (XV) with 98% $D_2SO_4$.

Kascheras[9] reacted 1-methylcyclopropylcarbinol (XVIII) with 50% $D_2SO_4$ at 160° and found aldehyde II and ketone III as the major products. Furthermore, the ketone III product was shown to be almost completely deuterated (see Table II, p. 6). Kascheras[9] proposed a protonated cyclopropane intermediate pathway to explain the extensive deuteration found in ketone III from the reaction of diol I with 50% $D_2SO_4$.

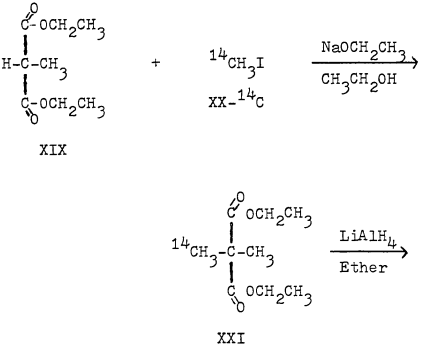
## Statement of the Problem

The objective of the work reported in this dissertation is to determine, through deuterium and carbon-14 labeling experiments, the mechanism by which 2,2-dimethyl-1,3-propanediol (I) rearranges in the presence of strong aqueous sulfuric acid to 2-methylbutanal (II) and 3-methyl-2-butanone (III).

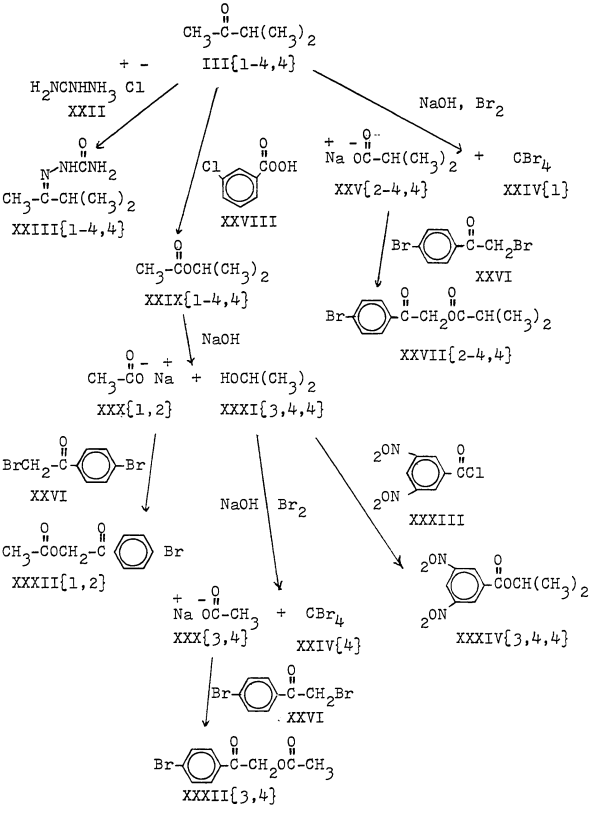
It was first necessary to confirm the results of Kascheras,[9] which implicated a protonated cyclopropane intermediate pathway. The previous experimental techniques[9] were considerably improved by 1) conducting the acid-catalyzed dehydration reaction under more controlled conditions of acidity and temperature, 2) use of 2,2-dimethyl-1,3-propanediol-$(OD)_2$ (Ia) to minimize protonic species caused by protonation from the reaction solution and 3) elimination of errors due to isotopic fractionation during gas chromatography in the deuterium-incorporation analysis of the 3-methyl-2-butanone (III) product.

The mechanism proposed by Kascheras[9] to account for 3-methyl-2-butanone (III-$d_{10}$) involves a rearrangement of the carbon skeleton. To investigate this point, 2,2-(dimethyl-$^{14}$C)-1,3-propanediol was synthesized and reacted with sulfuric acid. The resulting 3-methyl-2-butanone (III)[b1] (see p. 18) product was degraded to determine its carbon-14 distribution pattern. The synthetic and degradative paths are shown in Scheme IV, p. 16 and Scheme V, p. 17, respectively.

Scheme IV: Sysnthesis of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C).



Scheme V: Degradation of Carbon-14 Labeled 3-Methyl-2-butanone (III).



## Nomenclature

Many different deuterated and carbon-14 labeled 3-methyl-2-butanones (III) are referred to in this thesis. To distinguish them letters and numbers in brackets are used. In referring to the ketone III:

[a1] denotes ketone III from the reaction of 2,2-dimethyl-1,3-propanediol-$(OD)_2$ (Ia) with 55% deuteriosulfuric acid, p. 131.

[a2] denotes ketone III from the exchange reaction of 3-methyl-2-butanone (III) with $D_2O$, p. 140.

[a3] denotes ketone III from mixing equal volumes of 3-methyl-2-butanone (III)[a2] and undeuterated ketone III, p. 140.

[b1] denotes ketone III from the dehydration-rearrangement of 2,2-(dimethyl-$^{14}C$)-1,3-propanediol (I-$^{14}C$), p. 108.

[b2] denotes ketone III from the decarboxylation of methyl 2,2-(dimethyl-$^{14}C$)acetoacetate (XXXVI), p. 120.

[b3] denotes ketone III from the attempted isomerization of 3-methyl-2-butanone-4-$^{14}C$ (III)[b2] with 55% $H_2SO_4$, p. 125.

Each compound chemically derived from carbon-14 labeled 3-methyl-2-butanone (III) is named first according to the ketone III from which it is derived and second according to which of the carbon atoms of the ketone III it contains.

The ketone from which a compound is derived is denoted with a letter and a number in square brackets ([ ]) as described on the previous page. The carbon atoms of the ketone III which are contained in the compound are denoted by the ketone position numbers of said atoms in braces ({ }).

As an example: the degradation of 3-methyl-2-butanone (III)[b1], from the dehydration-rearrangement of 2,2-(dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) results in two p-bromophenacyl acetates (XXXII)[b1]. One results from the hydrolysis of isopropyl acetate (XXIX)[b1] and contains the C-1 and C-2 atoms of ketone III[b1]. It is denoted p-bromophenacyl acetate (XXXII)[b1]{1,2}. The other results from the bromoform reaction of isopropanol (XXXI)[b1]{3,4,4} and contains the C-3 and C-4 atoms of ketone III[b1]. It is denoted p-bromophenacyl acetate (XXXII)[b1]{3,4}.

## Results and Discussion

### I Dehydration of 2,2-Dimethyl-1,3-propanediol-$(OD)_2$ (Ia).

#### A) Procedure

The apparatus shown in Fig. I (p. 21) made it possible to study the acid-catalyzed dehydration-rearrangement of 2,2-dimethyl-1,3-propanediol (I) under more advantageous conditions than those previously used.[9] By employing a second pressure-equalizing addition funnel the rate of addition of water could be adjusted to maintain constant acidity without disturbing the uniform addition rate of diol I. By circulating oil from a large reservoir (14 l.), temperature equilibrium could be quickly attained and easily maintained. The substitiution of 2,2-dimethyl-1,3-propanediol-$(OD)_2$ (Ia) for undeuterated diol (I), which was used in the dehydration-rearrangement experiments of the previous deuterium work,[9] had the advantage of minimizing proton impurities in aldehyde II[al] and ketone III[al] caused by protonation from the reaction solution. The use of a total effluent gas chromatography collection system (see Appendix, p. 132) made it possible to quantitatively analyze samples for deuterium incorporation with excellent accuracy and precision.

All experiments were run in duplicate. Each of the entries in Table III, p. 22 and Table IV, p. 23, is the average of four determinations (duplicate mass spectra on each of two collected samples (glc)).

Figure I: Diol Reaction System.

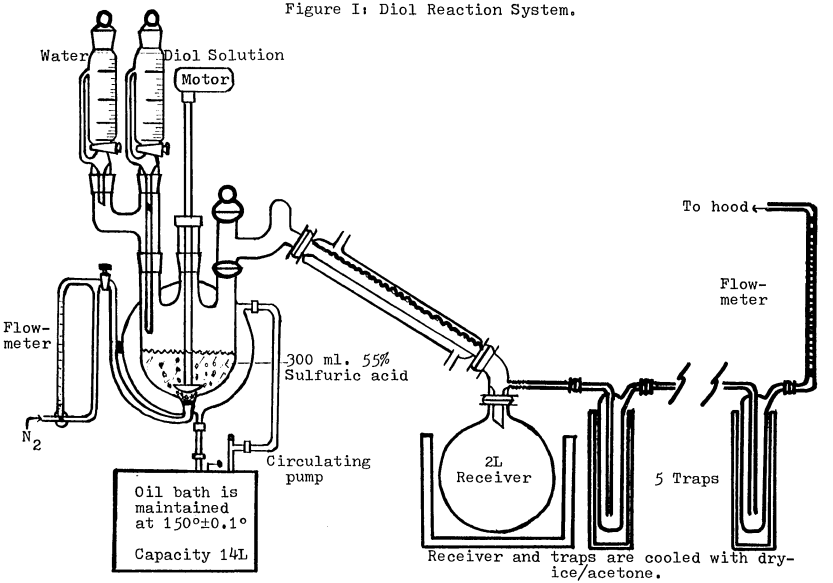


Table III: Percent Deuterium Incorporation and Isotopic Distribution in 2-Methylbutanal (II)[a1] from the Acid-Catalyzed-Dehydration-Rearrangement of 2,2-Dimethyl-1,3-propanediol-$(OD)_2$ (Ia) with 55% $D_2SO_4$.

| | | | Isotopic Distribution m/e%[a,b] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 86 | 87 | 88 | 89 | 90 | 91 |
| Sample | Run | % Deuterium Incorporation[b] | $d_0$ | $d_1$ | $d_2$ | $d_3$ | $d_4$ | $d_5$ |
| II[a1] | 1 | 19.7 | 1.9 | 28.3 | 49.0 | 14.1 | 4.7 | 1.9 |
| | 2 | 19.4 | 2.6 | 28.7 | 48.6 | 13.8 | 4.2 | 2.0 |
| II[c] | | 13.3 | 15.5 | 45.8 | 30.8 | 6.0 | 1.9 | 0.0 |

[a]Corrected for (M+1) contribution. [b]Each entry in Runs 1 and 2 is the average of four determinations (duplicate mass spectra on each of two collected samples (glc)). [c]Taken from reference 9, p. 14.

Table IV. Percent Deuterium Incorporation and Isotopic Distribution in 3-Methyl-2-butanone (III)[a1] from the Acid-Catalyzed Dehydration-Rearrangement of 2,2-Dimethyl-1,3-propanediol-$(OD)_2$ (Ia) with 55% $D_2SO_4$.

| Sample | Run | % Deuterium Incorporation | Isotopic Distribution m/e%[a,b] 86 ($d_0$) | 87 ($d_1$) | 88 ($d_2$) | 89 ($d_3$) | 90 ($d_4$) | 91 ($d_5$) | 92 ($d_6$) | 93 ($d_7$) | 94 ($d_8$) | 95 ($d_9$) | 96 ($d_{10}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| III[a1] | 1 | 80.7 | 0.5 | 0.5 | 0.8 | 1.7 | 2.1 | 8.8 | 7.3 | 18.3 | 6.8 | 11.4 | 42.0 |
| | 2 | 80.1 | 0.2 | 0.3 | 0.4 | 0.4 | 2.4 | 10.7 | 8.6 | 21.5 | 6.7 | 8.7 | 40.0 |
| III[c] | | 65.0 | 0.8 | 0.3 | 0.5 | 0.6 | 5.2 | 32.4 | 19.1 | 16.3 | 3.7 | 3.9 | 16.8 |

[a]Corrected for (M+1) contribution. [b]Each entry in Runs 1 and 2 is the average of four determinations (duplicate mass spectra on each of two collected samples (glc)). [c]Taken from reference 9, p. 18.

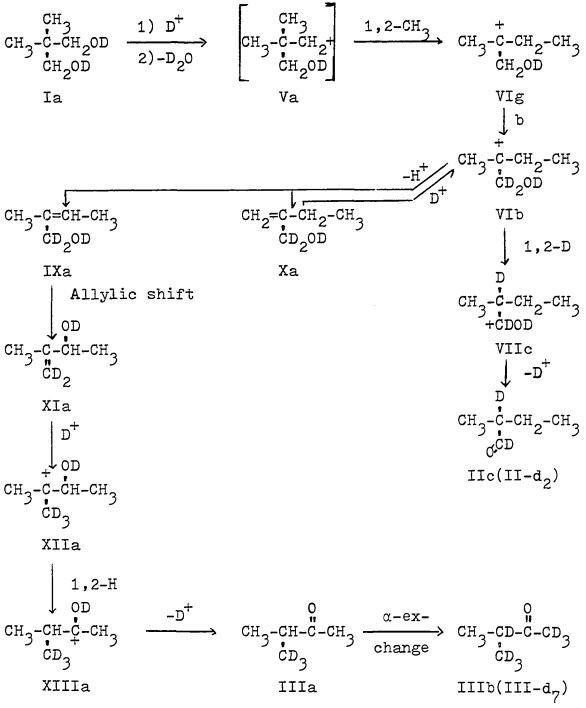
B) Results

The dropwise addition of a $D_2O$ solution of 2,2-dimethyl-1,3-propanediol-$(OD)_2$ (Ia) to 55% aqueous $D_2SO_4$ at 150°, while steam-distilling the volatile products through the use of a vigorous stream of nitrogen, resulted in the formation of 2-methylbutanal (II)[al] and 3-methyl-2-butanone (III)[al]. The isotopic distribution patterns of II[al] and III[al], as determined by mass spectral analysis, are presented in Table III, p. 22, and Table IV, p. 23, respectively. The patterns show the same general trends as the ones obtained by Kascheras[9] in the dehydration-rearrangement of 2,2-dimethyl-1,3-propanediol (I) with 50% $D_2SO_4$ at 160°.

In agreement with the results of Kascheras,[9] 2-methylbutanal (II)[al] consisted of mainly $d_1$ and $d_2$ species (Table I, p. 5). These species could be accommodated by Mechanism IIb, p. 25, in which II-$d_2$ is formed through the reversal of steps VIg → IIc (Scheme Ib, p. 26). Kascheras[9] reacted aldehyde II with 50% $D_2SO_4$ and recovered II and ketone III as products. The pattern of isotopic distribution in III (Table II, p. 6) was similar to that obtained in III from the reaction of I with 50% $D_2SO_4$,[9] indicating that III formed from II through Mechanism IIb, p. 25, and Scheme Ib, p. 26. The greater contribution of II-$d_2$ in the present study compared to that found by Kascheras[9] (Table III, p. 22) indicates that the reactions of Scheme Ib played a greater role in aldehyde II formation in the present work.

2-Methylbutanal (II)[al] consisted of larger contribu-

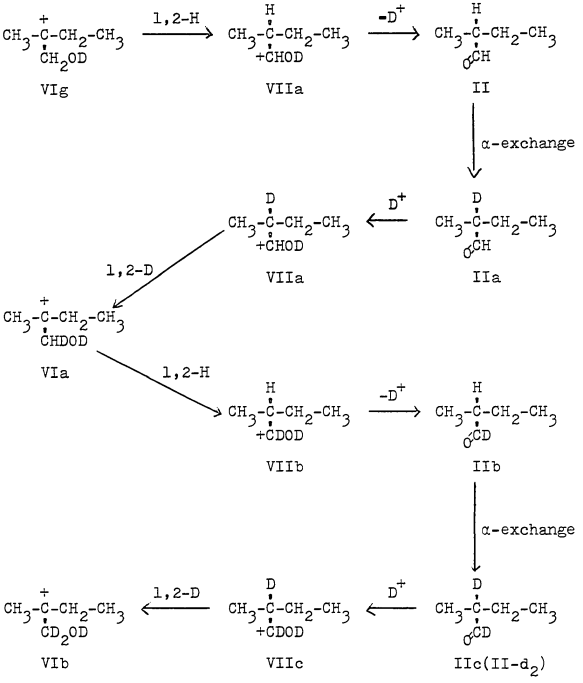
Mechanism IIb: Formation of 2-Methylbutanal (II-$d_2$) and 3-Methyl-2-butanone (III-$d_7$) through the Allylic Shift Pathway in the $D_2SO_4$-Catalyzed Dehydration-Rearrangement of 2,2-Dimethyl-1,3-propanediol-(OD)$_2$ (Ia).




[a]See footnote, Mechanism I, p. 3.

[b]See Scheme Ib, p. 26.

Scheme Ib: Formation of 2-Methylbutanal (II-$d_2$) and VIb From Intermediate VIg.[a]




[a]See Scheme I, p. 8 and Mechanism IIb, p. 25.

tions from the $d_3$-$d_5$ species in the present study (Table III, p. 22) compared to the previous work.[9] These species can arise through Mechanism IIb, p. 25, with the intervention of Scheme II, p. 10 and Scheme Ia, p. 11 (see pages 9 and 10). The combination of Schemes II and Ia allows for the incorporation in aldehyde II of from three to five deuterium atoms with a labeling pattern of $d_3 > d_4 > d_5$, as is found.

In agreement with the results of Kascheras[9] 3-methyl-2-butanone III[al] consisted mainly of $d_5$-$d_{10}$ species (Table IV, p. 23). The allylic shift pathway (see p. 9) predicts the incorporation of 5 deuterium atoms in ketone III and Scheme I, p. 8, could be invoked to account for $d_6$ and $d_7$ species (see p. 9). The larger contribution made by $d_6$ and $d_7$ species relative to $d_5$ (Table IV, p. 23) constitutes further evidence that the reactions of Scheme Ib played a greater role in product formation in the present work (see p. 24) compared to that of Kascheras.[9]

As in the previous work,[9] it is the pattern of deuterium incorporation in ketone III above $d_7$ that is of most interest. The contribution made by the III-$d_8$ and III-$d_9$ species is not major, in contrast to the III-$d_{10}$ species which is the most abundant product. The finding, in the present work, of a substantial amount of II-($d_3$-$d_5$) (Table III, p. 22) warranted a reconsideration of Scheme II, p. 10, as a source of ketone III-($d_8$-$d_{10}$) (see p. 10, and Mechanism IIb, p. 25).

However, the absence of a major contribution by aldehyde II-$d_5$ (Table III, p. 22) indicates that the reversal of step

VI → X (Scheme II, p. 10) is not the major source of ketone III-$d_{10}$. The labeling pattern in aldehyde II is $d_3 > d_4 > d_5$ while the labeling pattern in ketone III is $d_8 < d_9 << d_{10}$. Since some $d_5$ aldehyde II is formed, a minor amount of ketone III-$d_{10}$ probably arises by this route. The greater amount of II-$d_3$ and II-$d_4$ (relative to II-$d_5$) formed suggests that Scheme II, p. 10, has greater importance in the formation of III-$d_8$ and III-$d_9$, in particular the former species.

The greater contribution made by III-$d_{10}$ found here, compared to that found in the previous work,[9] indicates that a mechanism (or mechanisms) other than Mechanism I, p. 3, played a greater role in product formation in the present work.

The isotope distribution patterns of aldehyde II (Table III, p. 22) and ketone III (Table IV, p. 23) (see page 24 and 27) indicate that Scheme I, p. 8, and Scheme II, p. 10, played a greater role in product formation in the present study, compared to the work of Kascheras.[9] The previous work[9] was done in 58.2% (w/w) $D_2SO_4$ at 160° while the present work was done in 70.2% (w/w) $D_2SO_4$ at 150°. The flow of nitrogen, which continuously removed the volatile products from the reaction mixture, was also different. These differences in reaction conditions in the two studies probably account for the different extents to which Scheme I and Scheme II are involved in both aldehyde II and ketone III formation. The different reaction conditions in the two studies probably also account for the greater role played by the mechanism(s) leading to ketone III-$d_{10}$ in the present study.

II Dehydration-Rearrangement of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C).

A) Procedure

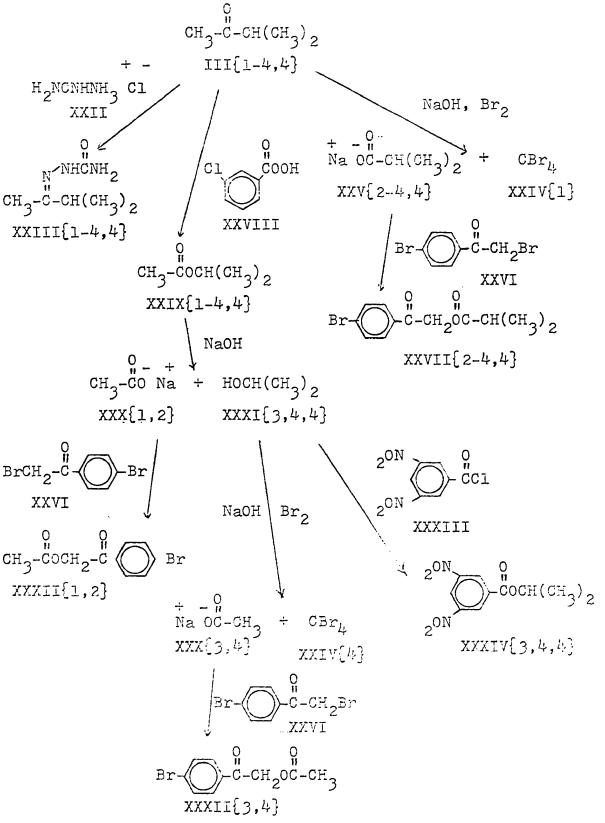
The synthesis of 2,2-(dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) is shown in Scheme IV, p. 16. The degradation of 3-methyl-2-butanone (III)[b1] is shown in Scheme V, p. 17 and again here on p. 30.

Gas chromatography proved more sensitive than proton magnetic resonance to chemical impurities for ketone III and was used to estimate purity. Radiochemical purity of ketone III was established by a comparison of the molar activity of III with that of its semicarbazone derivative (XXIII), which was recrystallized to constant activity.

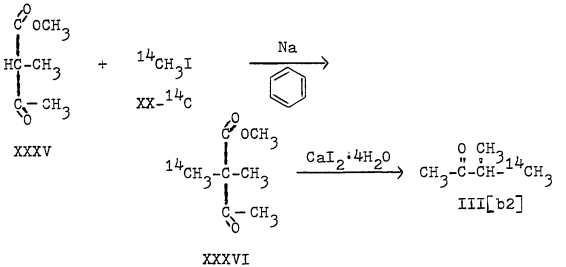
Counting efficiency was generally between 80% and 90% with a modified Bray's solution as the scintillation solvent (see p. 98). Samples were counted long enough to produce an instrument counting error of less than 1%. Derivatives were recrystallized until consecutive molar activity determinations agreed within 1%.

In order to determine if the degradation of 3-methyl-2-butanone (III)[b1] (Scheme V, p. 30) produced any carbon-14 label rearrangement, 3-methyl-2-butanone-4-$^{14}$C (III)[b2] was synthesized (Scheme VI, p. 31) and degraded according to Scheme V. Glc detected less than 1% impurity in ketone III [b2]. Radiochemical purity (see above) of III[b2] was found to be greater than 99%.

Scheme V: Degradation of Carbon-14 Labeled 3-Methyl-2-butanone (III).



Scheme VI: Synthesis of 3-Methyl-2-butanone (III)[b2].



XXXV

XXXVI

The molar activity of semicarbazone XXIII[b2]{1-4,4} (Table V, p. 32) and the derivatives containing both C-4 methyl groups of ketone III[b2], p-bromophenacyl isobutyrate (XXVII)[b2]{2-4,4} and isopropyl 3,5-dinitrobenzoate (XXXIV)[b2]{3,4,4}, are all the same (± 0.8%). p-Bromophenacyl acetate (XXXII)[b2]{3,4} and $CBr_4$ (XXIV)[b2]{4} each contain one of the two C-4 methyl groups of ketone III[b2]. As expected, therefore, the molar activity of each is half (50.2% and 50.5%, respectively) that of XXIII[b2]{1-4,4}. Although $CBr_4$ (XXIV)[b2]{1} had some activity (4.3%), it was considered spurious since XXVII[b2]{2-4,4}, prepared in the same reaction, contained all of the activity found in XXIII[b2]{1-4,4} and also since p-bromophenacyl acetate (XXXII)[b2]{1,2} had no significant activity. The sum of the molar activities of XXXII[b2]{3,4} and XXIV[b2]{4} (Table V, p. 32) is, within 1%, the same as both the molar activity of XXXIV[b2]{3,4,4} and of XXIII[b2]{1-4,4}.

Table V: Molar Activities and Percent XXIII Values[a] for 3-Methyl-2-butanone-4-$^{14}$C (III)[b2], III[b3] and their Derivatives.

| Compound | [b2] Activity in μc./mole | [b2] % XXIII Value | [b3] Activity in μc./mole | [b3] % XXIII Value |
|---|---|---|---|---|
| 3-Methyl-2-butanone (III) | 432.0[b,c] | 99.6 | 476.3±0.6[c] | 100.6 |
| Semicarbazone (XXIII){1-4,4} of Ketone III | 433.9±0.7 | (100.0) | 473.4±0.6 | (100.0) |
| Carbon tetrabromide (XXIV){1} | 18.6±0.0 | 4.3 | 22.2±0.0 | 4.7 |
| p-Bromophenacyl Acetate (XXXII){1,2} | 0.66 ±0.01 | 0.15 | 0.35 ±0.0 | 0.74 |
| p-Bromophenacyl Isobutyrate (XXVII){2-4,4} | 440.6±0.5 | 101.5 | 472.6±0.7 | 99.8 |
| Isopropyl 3,5-Dinitrobenzoate (XXXIV){3,4,4} | 437.9±0.1 | 100.9 | 474.1±0.1 | 100.1 |
| p-Bromophenacyl Acetate (XXXII){3,4} | 217.8±0.2 | 50.2 | 237.1±0.2 | 50.1 |
| Carbon tetrabromide (XXIV){4} | 219.2±0.2 | 50.5 | 241.2±0.3 | 51.0 |

[a]Molar activity divided by the molar activity of the semicarbazone XXIII derivative x 100.
[b]Only one determination was made.
[c]The molar activity of III[b3] derivatives are greater than those of III[b2] because III [b2] was slightly diluted prior to degradation (see p. 116).

For convenience the molar activities in Table V, p. 32, were translated into % XXIII values which represent one hundred multiplied by the ratio of the molar activity of any derivative to the molar activity of the semicarbazone derivative XXIII{1-4,4} of the same ketone III.

To insure that the values for molecular activity and % XXIII of the derivatives of ketone III[b2] are valid, internal consistencies in the degradation scheme were sought. The molecular activity (or % XXIII value) of a derivative must be equal to the sum of the molar activities (or % XXIII values) of two other derivatives of the same ketone III if the former contains the same carbon atoms as both the latter two together. For example: the % XXIII value of XXIII[b2]{1-4,4} should be equal to the sum of the % XXIII values of XXXII[b2]{1,2} and XXXIV[b2]{3,4,4}. And indeed, this is the case as can be seen in Table VI, p. 34.

It may be concluded from comparisons of the molar activities in Table V, p. 32 and the % XXIII values in Table VI, p. 34 that 3-methyl-2-butanone-4-$^{14}$C (III)[b2] was degraded, according to Scheme V, p. 30, without carbon-14 rearrangement. Scheme V, therefore, could be used to determine carbon-14 distribution in ketone III[b1] from the sulfuric acid-catalyzed dehydration-rearrangement of 2,2-(dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C).

Fry[15] had reported on the acid-catalyzed rearrangement of α-branched alkyl ketones, and, more recently, has found[16] that 3-methyl-2-butanone-1-$^{14}$C rearranges to 3-methyl-2-

Table VI: Internal Consistancies in the Degradation of 3-Methyl-2-butanone (III).[a]

| Compounds | Percent XXIII Values[b] [b1] Run 1 | Run 2 | [b2] | [b3] |
|---|---|---|---|---|
| 3-Methyl-2-butanone (III) | 101.2 | 100.5 | 99.6 | 100.6 |
| XXIII {1-4,4} | (100.0) | (100.0) | (100.0) | (100.0) |
| XXIV {1} + XXVII {2-4,4} | 101.5 | 98.97 | 105.8 | 104.5 |
| XXXII {1,2} + XXXIV {3,4,4} | 101.6 | 100.7 | 101.0 | 100.8 |
| XXXIV {3,4,4} | 52.96 | 52.82 | 100.9 | 100.1 |
| XXXII {3,4} + XXIV {4} | 52.79 | 52.86 | 100.7 | 101.1 |

[a]See Table V, p. 32, and Table VII, p. 38.
[b]See Footnote a, Table V, p. 32.

butanone-4-$^{14}$C. If this carbon-14 rearrangement occurred in ketone III[b1] after it formed in the reaction vessel, it would not be possible to ascertain the carbon-14 distribution in III[b1] due solely to its formation from diol I-$^{14}$C. Therefore, it was considered necessary to test the stability of ketone III to rearrangement under the reaction conditions.

3-Methyl-2-butanone-4-$^{14}$C (III)[b2] was added dropwise, under essentially the same conditions as used for diol I-$^{14}$C, to 55% sulfuric acid at 150°. The organic extract containing the crude product was concentrated and refluxed with silver oxide (p. 108) for 18 hr. in order to remove any aldehyde II[b3] that may have formed. The organic extract containing ketone III[b3] was dried, filtered and distilled. 3-Methyl-2-butanone (III)[b3] was found to contain less than 1% chemical impurity. Radiochemical purity (p. 29), as determined from the values in Table V, p. 32 was greater than 99%.

In Table V, p. 32, the % XXIII values of XXIII[b3]{1-4,4}, XXVII[b3]{2-4,4} and XXXIV[b3]{3,4,4} are all the same (± 0.2%). Furthermore, XXIV[b3]{4} and XXXII[b3]{3,4} each contain half (50.1% and 51.0%) of the activity of XXIII[b3]{1-4,4}. Once again, the $CBr_4$ (XXIV){1} derivative contained activity. However, since XXVII[b3]{2-4,4} contained all of the activity of XXIII[b3]{1-4,4} and XXXII[b3]{1,2} had no significant activity, the activity (4.7%) in $CBr_4$ (XXIV)[b3]{1} was considered spurious. The sum of the % XXIII values of XXXII[b3]{3,4} and XXIV[b3]{4} and the % XXIII value of XXXIV[b3]{3,4,4} and the % XXIII value of

XXIII[b3]{1-4,4} are the same, within 1.1% (Table VI, p. 34).

It may be concluded from comparisons of molar activities in Table V, p. 32, that all of the carbon-14 in ketone III [b3] was contained in the C-4 methyl groups. In comparing the % XXIII values in the III[b2] and III[b3] derivatives (Table V, p. 32), there are no significant differences in C-1 containing or C-4 containing derivatives. It may be concluded, therefore, that under our reaction conditions labeled ketone III does not undergo carbon-14 scrambling.

The distribution of carbon-14 label in 3-methyl-2-butanone (III)[b1], as determined by degradative Scheme V, p. 30, is due solely to the sulfuric acid-catalyzed dehydration-rearrangement of 2,2-(dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C).

B) Results

The dropwise addition of an aqueous solution of 2,2-(dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) to 55% $H_2SO_4$ at 150°, while steam-distilling the volatile products through the use of a vigorous stream of nitrogen, resulted in the formation of the above-mentioned carbonyl-containing products: 2-methyl-butanal (II)[b1] and 3-methyl-2-butanone (III)[b1]. Aldehyde II[b1] was destroyed by refluxing with silver oxide (p. 108. Ketone III[b1] was degraded as described in Scheme V, p. 30. The entire reaction sequence involving the dehydration-rearrangement of diol I-$^{14}$C and the degradation of isolated ketone III[b1] was carried out in duplicate. The chemical purity of III[b1] from runs 1 and 2 was 98.9% and 99.5%, respectively. The radiochemical purity (see p. 29) of III[b1] from the two runs was calculated to be 98.8% and 99.0%.

The molar activities of III[b1] and its derivatives and their % XXIII values (see p. 33) are shown in Table VII, p. 38. The ketones III[b1] from the two dehydration-rearrangements of diol I-$^{14}$C were diluted to different extents prior to degradation and therefore have different molar activities. It is therefore, more convenient to consider the derivatives of ketone III[b1] in terms of their % XXIII values.

Internal consistencies (see p. 33) in the % XXIII values of the degradation of ketone III[b1] are shown in Table VI, p. 34. The sum of the % XXIII values of derivatives XXIV[b1]{1} and XXVII[b1]{2-4,4} is the same as that for the semicarbazone XXIII[b1]{1-4,4} (± 1.5% for run 1 and ± 1.0% for run

Table VII: Molar Activities and Percent XXIII Values[a] for 3-Methyl-2-butanone (III)[b1] and its Derivatives.

| Compound | [b1] Run 1 Activity in μc./mole | [b1] Run 1 % XXIII Value | [b1] Run 2 Activity in μc./mole | [b1] Run 2 % XXIII Value |
|---|---|---|---|---|
| 3-Methyl-2-butanone (III) | 843.8±0.4[b] | 101.2 | 241.9±0.5[b] | 100.5 |
| Semicarbazone (XXIII) {1-4,4} of Ketone III | 833.7±0.2 | (100.0) | 240.8±0.3 | (100.0) |
| Carbon tetrabromide (XXIV){1} | 378.8±0.5 | 45.44 | 103.1±0.1 | 42.82 |
| p-Bromophenacyl Acetate (XXXII){1,2} | 401.8±0.8 | 48.20 | 115.4±0.1 | 47.92 |
| p-Bromophenacyl Isobutyrate (XXVII){2-4,4} | 467.8±0.2 | 56.11 | 135.2±0.2 | 56.15 |
| Isopropyl 3,5-Dinitrobenzoate (XXXIV){3,4,4} | 441.5±0.4 | 52.96 | 127.2±0.4 | 52.82 |
| p-Bromophenacyl Acetate (XXXII){3,4} | 223.0±0.3 | 26.74 | 65.0±0.1 | 26.99 |
| Carbon tetrabromide (XXIV){4} | 217.0±0.2 | 26.03 | 62.3±0.1 | 25.87 |

[a]Molar activity divided by the molar activity of the semicarbazone XXIII derivative x 100.
[b]The molar activities of III[b1] derivatives for runs 1 and 2 are different because ketones III[b1] were diluted to different extents prior to degradation (see p. ).

2). The same is the case for the sum of % XXIII values for derivatives XXXII[bl]{1,2} and XXXIV[bl]{3,4,4} (± 1.6% for run 1 and ±0.7% for run 2). Furthermore, the sum of the % XXIII values for XXXII[bl]{3,4} and XXIV[bl]{4} is equal to that of XXXIV[bl]{3,4,4} (± 0.3% for run 1 and ± 0.1% for run 2). These internal consistencies indicate that the reported values of the activities in Table VII, p. 38, are reliable.

The percentage of carbon-14 label in the different positions of 3-methyl-2-butanone (III)[bl] is calculated from the % XXIII values of Table VII, p. 38, and is based on the average of at least two calculations (see below and also Scheme V, p. 30).

The percentage of carbon-14 label in the C-1 position of III[bl], shown in Table VIII, p. 40, is calculated as equal to the % XXIII value (see p. 33) of $CBr_4$ (XXIV)[bl]{1} and also as the difference in % XXIII values of the semicarbazone XXIII[bl]{1-4,4} and the ester XXVII[bl]{2-4,4}.

The percent of carbon-14 label in the C-2 position of III[bl] is calculated in three ways (Table IX, p. 41). The first way is the difference in % XXIII values of ester XXXII [bl]{1,2} and $CBr_4$ (XXIV)[bl]{1} and the second is the difference in % XXIII values of esters XXVII[bl]{2-4,4} and XXXIV [bl]{3,4,4}. The third way is the difference in % XXIII values between the semicarbazone XXIII[bl]{1-4,4} and the sum of esters XXVII[bl]{2-4,4} and XXXII[bl]{1,2}.

Table X, p. 42, shows the three different calculations for the percent carbon-14 label in the C-3 position of III

Table VIII: Percent Carbon-14 Label in the C-1 Position of 3-Methyl-2-butanone (III)[b1]

| Calculation | Run | {C-1} (% XXIII Value[a]) |
|---|---|---|
| {1} | 1 | 45.44 |
| | 2 | 42.82 |
| {1-4,4} - {3,4,4} | 1 | 100.0 - 56.11 = 43.89 |
| | 2 | 100.0 - 56.15 = 43.85 |
| Average {C-1} | | 44.0±0.7 |

[a]See footnote a, Table V, p. 32.

Table IX: Percent Carbon-14 Label in the C-2 Position of 3-Methyl-2-butanone (III)[b1]

| Calculation | Run | {C-2} (% XXIII Value[a]) |
|---|---|---|
| {1,2} - {1} | 1 | 48.20 - 45.44 = 2.76 |
| | 2 | 47.92 - 42.82 = 5.10 |
| {2-4,4} - {3,4,4} | 1 | 56.11 - 52.96 = 3.15 |
| | 2 | 56.15 - 52.82 = 3.33 |
| {2-4,4} + {1,2} - {1-4,4} | 1 | 56.11 + 48.20 - 100.0 = 4.31 |
| | 2 | 56.15 + 47.92 - 100.0 = 4.07 |
| Average {C-2} | | 3.8±0.7 |

[a]See footnote a, Table V, p. 32.

Table X: Percent Carbon-14 Label in the C-3 Position of 3-Methyl-2-butanone (III)[b1]

| Calculation | Run | {C-3} (% XXIII Value[a]) |
|---|---|---|
| {3,4} - {4} | 1 | 26.74 - 26.03 = 0.71 |
| | 2 | 26.99 - 25.87 = 1.12 |
| 2{3,4} - {3,4,4} | 1 | 2(26.74) - 52.96 = 0.52 |
| | 2 | 2(26.99) - 52.82 = 1.16 |
| {3,4,4} - 2{4} | 1 | 52.96 - 2(26.03) = 0.90 |
| | 2 | 52.82 - 2(25.87) = 1.08 |
| Average {C-3} | | 0.90±0.2 |

[a]See footnote a, Table V, p. 32.

[bl]. The first is the difference in % XXIII values of the ester XXXII[bl]{3,4} and $CBr_4$ (XXIV)[bl]{4}. The second is the difference in two times the % XXIII value of ester XXXII [bl]{3,4} and the % XXIII value of XXXIV[ bl ]{3,4,4}. The third determination was calculated as the difference in the % XXIII value of XXXIV[bl]{3,4,4} and two times the % XXIII value of $CBr_4$ (XXIV)[bl]{4}.

The percent carbon-14 label in the C-4 position of III [bl] (Table XI, p. 44) is calculated as equal to two times the % XXIII value of XXIV[bl]{4} and also as two times the difference in % XXIII values of esters XXXIV[bl]{3,4,4} and XXXII[bl]{3,4}.

The average values for the percent of carbon-14 label in each of the positions of ketone III[bl] (Tables VIII through XI) are normalized in Table XII, p. 45. The normalized percent carbon-14 label distribution in 3-methyl-2-butanone (III)[bl] is 43.7 ± 0.7, 3.8 ± 0.7, 0.9 ± 0.2 and 51.6 ± 0.3 for the C-1, C-2, C-3 and C-4 positions, respectively.

Table XIII, p. 46, gives the expected carbon-14 label distribution in 3-methyl-2-butanone (III)[bl] from the acid-catalyzed dehydration-rearrangement of 2,2-(dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) as a function of various mechanisms (to be discussed later). The allylic shift pathway (Mechanism I-$^{14}$C, p. 47) would distribute all of the carbon-14 label equally between the C-1 and C-4 positions of ketone III[bl]. Incorporation of carbon-14 label in the C-2 and C-3 positions of ketone III[bl] requires the formation of

Table XI: Percent Carbon-14 Label in the C-4 Position of 3-Methyl-2-butanone (III)[b1]

| Calculation | Run | $2\{C\text{-}4\}^{a}$ (% XXIII Value[b]) |
|---|---|---|
| $2\{4\}$ | 1 | $2(26.03) = 52.06$ |
| | 2 | $2(25.87) = 51.74$ |
| $2(\{3,4,4\} - \{3,4\})$ | 1 | $2(52.96 - 26.74) = 52.44$ |
| | 2 | $2(52.84 - 25.87) = 51.66$ |
| Average $2\{C\text{-}4\}$ | | $52.0 \pm 0.3$ |

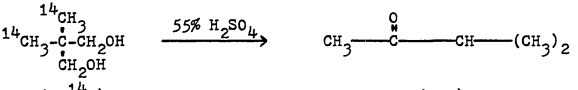
[a]There are 2 C-4 position atoms in the ketone III[b1] molecule.
[b]See footnote a, Table V, p. 32.

Table XII: Normalized Values for the Percent Carbon-14 Distribution in 3-Methyl-2-butanone (III)[b1]

| Position | $CH_3$—$\overset{O}{\overset{\|}{C}}$—CH—$(CH_3)_2$ {C-1} | {C-2} | {C-3} | {C-4} |
|---|---|---|---|---|
| Average Value[a] | 44.0±0.7 | 3.8±0.7 | 0.9±0.2 | 52.0±0.3 |
| Normalized Value | 43.7±0.7 | 3.8±0.7 | 0.9±0.2 | 51.6±0.3 |

[a]See Tables VIII through XI.

Table XIII: Expected Carbon-14 Distribution in 3-Methyl-2-butanone (III) from the Sulfuric Acid-Catalyzed Dehydration-Rearrangement of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) as a Function of Mechanism

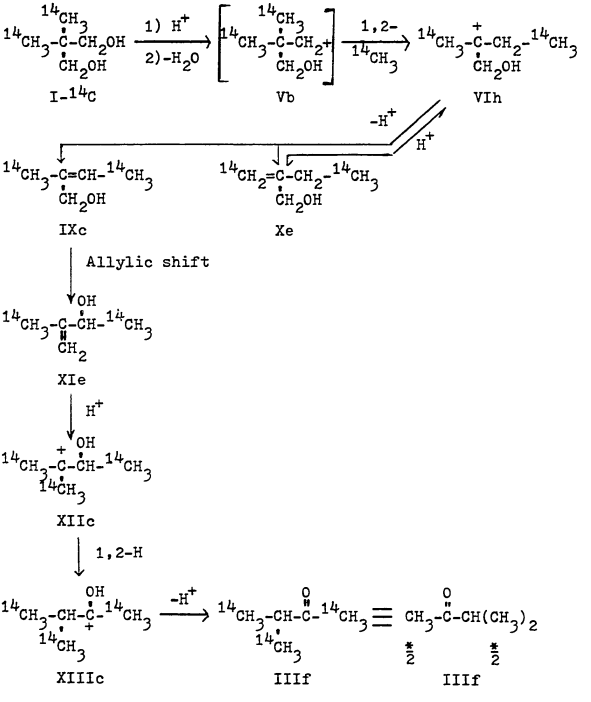



(I-$^{14}$C) (III)

| Mechanism | {C-1} | {C-2} | {C-3} | {C-4} |
|---|---|---|---|---|
| (Experimental Values[a]) | 43.7± 0.7 | 3.8± 0.7 | 0.9± 0.2 | 51.6± 0.3 |
| Mechanism I-$^{14}$C(p. 47) | 50.0 | | | 50.0 |
| Mechanism VI(Path A)(p. 67) | 25.0 | 25.0 | | 50.0 |
| (Path B)(p. 68) | 25.0 | 12.5 | | 62.5 |
| (Path C)(p. 69) | 16.67 | 16.67 | | 66.67 |
| Mechanism VIII(Path A)(p. 74) | 25.0 | | 25.0 | 50.0 |
| (Path B)(p. 75) | 31.25 | | 12.5 | 56.25 |
| (Path C)(p. 76) | 33.33 | | 16.67 | 50.0 |
| Mechanism IX(p. 77) | | | | 100.0 |
| Mechanism X(p. 78) | 50.0 | | | 50.0 |

[a]See Table XII, p. 32.

Mechanism I-$^{14}$C: Formation of 3-Methyl-2-butanone (III) through the Allylic Shift Pathway[a] in the Sulfuric Acid-Catalyzed Dehydration-Rearrangement of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C).




I-$^{14}$C Vb VIh IXc Xe XIe XIIc XIIIc IIIf IIIf

[a]See Mechanism I, p. 3.

some III[b1] through a mechanism other than the allylic shift pathway.

The conclusions from our deuterium labeling studies is confirmed; the allylic shift pathway (Mechanism I) is not the only mechanism involved in the formation of 3-methyl-2-butanone (III) from the sulfuric acid-catalyzed dehydration-rearrangement of 2,2-dimethyl-1,3-propanediol (I).

III Mechanisms

A) Cyclopropane Pathway

In searching for a mechanism that could account for the observed proton exchange (see p. 14) in the formation of 3-methyl-2-butanone (III), Kascheras[9] considered the possible intervention of protonated cyclopropane intermediates. The two cyclopropanes that can form from diol I are shown in Scheme VII, p. 50. Depuy and coworkers[17] have shown that cyclopropanols tend to ring-open in acid media to give carbonyl compounds. When 2,2-dimethylcyclopropanol (XLI) was reacted with 50% $D_2SO_4$ at 160°,[9] a mixture of 2,2-dimethylpropanal (XLII),[a] 3-methylbutanal (XLIII) and ketone III was formed. While III was the major product, nmr spectroscopy indicated it was not extensively deuterated. Since XLIII was not found among the reaction products from diol I and since the ketone III from I is extensively deuterated (see Table II, p. 6 and again here on p. 51), XLI can be ruled out as the major intermediate leading to III-$d_{10}$.

Cyclopropylmethyl derivatives solvolyze readily yielding rearranged and position-scrambled products.[18,19,20,21] Three types of rearrangements occur: 1) ring expansion to cyclobutyl products, 2) ring opening to 3-butenyl products and 3) rearrangement through a degenerate intermediate to carbon-scrambled cyclopropylmethyl products.

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[a] 2,2-Dimethylpropanal (XLII) has been shown to react with 50% $H_2SO_4$ at 160° to form ketone III.[9]

Scheme VII: Formation of Cyclopropane Systems from 2,2-Dimethyl-1,3-propanediol (I).

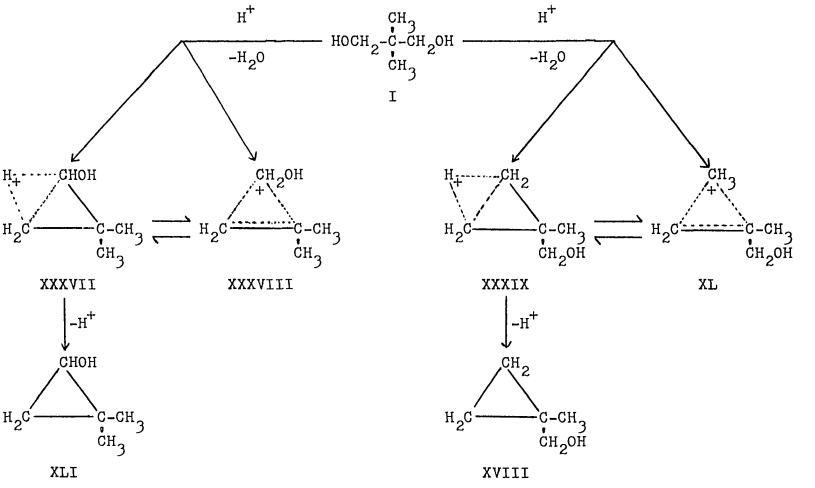


Table II: Percent Deuterium Incorporation and Isotopic Distribution in 3-Methyl-2-butanone (III) from Reactions in 50% $D_2SO_4$.[a]

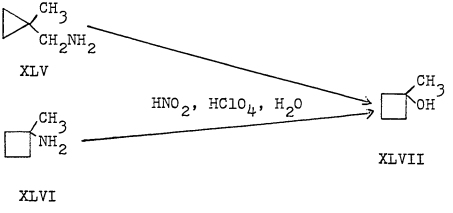
| | Reactant | % Deuterium Incorporation | Isotopic Distribution m/e%[b] 86 ($d_0$) | 87 ($d_1$) | 88 ($d_2$) | 89 ($d_3$) | 90 ($d_4$) | 91 ($d_5$) | 92 ($d_6$) | 93 ($d_7$) | 94 ($d_8$) | 95 ($d_9$) | 96 ($d_{10}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $(CH_3)_2C(CH_2OH)_2$ | 65.0 | 0.8 | 0.3 | 0.5 | 0.6 | 5.2 | 32.4 | 19.1 | 16.3 | 3.7 | 3.9 | 16.8 |
| II | $CH_3-CH_2-\underset{CH_3}{\overset{O}{\overset{\|}{C}}}-CH$ | 70.9 | 0.9 | 1.7 | 2.3 | 1.3 | 2.9 | 5.9 | 20.6 | 31.2 | 6.4 | 7.8 | 18.5 |
| III | $CH_3-\underset{CH_3}{\overset{O}{\overset{\|}{C}}}-C-CH_3$ | 38.9 | 0.7 | 1.4 | 2.1 | 4.7 | 90.3 | 0.0 | 0.1 | 0.7 | 0.0 | 0.0 | 0.0 |
| IX | $CH_3-C=CH(OH)-CH_3$ <br> $CH_2OH$ | 51.9 | 1.3 | 1.4 | 1.2 | 1.2 | 6.7 | 74.5 | 3.5 | 2.5 | 1.2 | 1.1 | 5.4 |
| XI | $CH_2=C-CH_2-CH_3$ <br> $CH_2OH$ | 50.6 | 1.0 | 1.2 | 0.9 | 1.2 | 8.1 | 78.0 | 3.1 | 1.5 | 0.8 | 0.8 | 3.4 |
| XVIII |  <br> $CH_2OH$ | 95.5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.3 | 0.9 | 2.7 | 8.5 | 24.5 | 63.0 |
| XLIV | $HOCH_2-C(OH)-CH_2-CH_3$ <br> $CH_3$ | 64.3 | 0.1 | 0.8 | 1.1 | 1.6 | 5.6 | 29.4 | 16.2 | 23.8 | 4.4 | 3.2 | 13.8 |
| XLIX | $CH_2=C-CH_2-CH_2OH$ <br> $CH_3$ | 93.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.2 | 0.7 | 2.7 | 4.9 | 9.4 | 20.6 | 61.5 |

[a]Taken from reference 9, p. 18. [b]Corrected for (M+1) contribution.

When 1-methylcyclopropylcarbinol (XVIII) was reacted with 50% $D_2SO_4$ at 160°,[9] ketone III, aldehyde II, and a trace of 2,2-dimethylpropanal (XLII) were obtained. The ketone III product was shown by mass spectral analysis to be very extensively deuterated, (Table II, p. 51). When 2-methyl-1,2-butanediol(XLIV) was reacted with 50% $D_2SO_4$, the isotopic distribution pattern in the ketone III product was similar to that in ketone III[bl] from the reaction of diol I with 50% $D_2SO_4$ (Table II, p. 51). Diol XLIV would be expected to give cation VI upon protonation and loss of water. It is possible, therefore, that cation VI is also a source of cyclopropane XVIII from diol I.

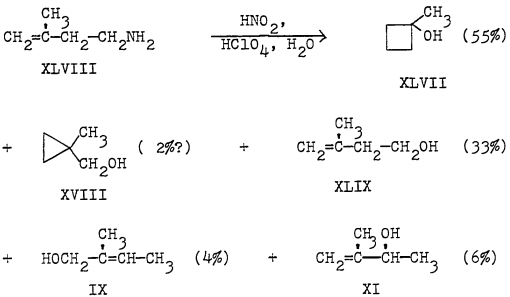
Roberts and coworkers[20] have studied the 1-methylcyclopropylmethyl system in some detail. They observed that (1-methylcyclopropyl)carbinylamine (XLV) and 1-methylcyclobutylamine (XLVI) upon reaction with nitrous acid in aqueous perchloric acid yielded exclusively 1-methylcyclobutanol (XLVII) (see Scheme VIII).

Scheme VIII: Nitrous Acid Deamination of (1-Methylcyclopropyl)-carbinylamine (XLV) and 1-Methylcyclobutylamine (XLVI).

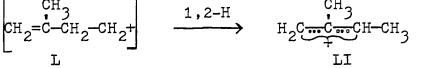


Nitrous acid deamination of 3-methyl-3-butenylamine (XLVIII) in aqueous perchloric acid yielded a mixture of alcohols (see Scheme IX) identified as 55% XLVII, 2% (±2%)

Scheme IX: Nitrous Acid Deamination of 3-Methyl-3-butenylamine (XLVIII).




1-methylcyclopropylcarbinol (XVIII), 33% 3-methyl-3-buten-1-ol (XLIX), 4% IX and 6% XI.[20] The authors suggested that the unsaturated open-chain alcohols are derived from the 3-methyl-3-butenyl cation (L), which could react with solvent or undergo a 1,2-hydride shift to form the resonance stabilized 1,2-dimethylallyl cation (LI). Reaction of LI with water would be expected to yield both IX and XI.



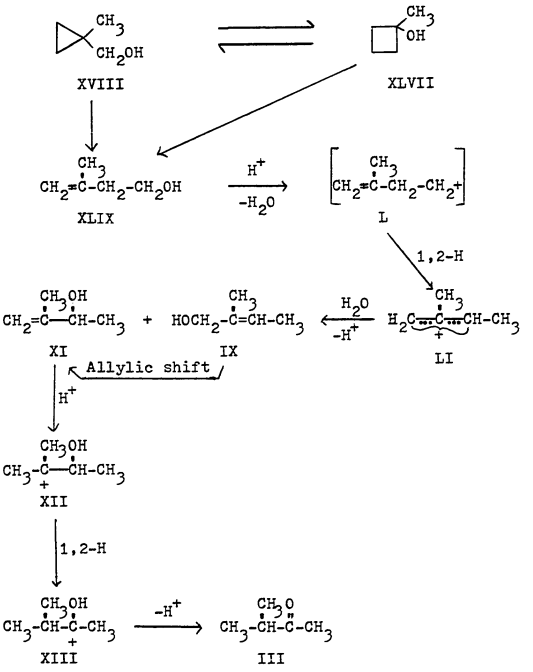

Allylic alcohols IX and XI (see Scheme IX) are both

intermediates in the allylic shift pathway (Mechanism I, p. 3) and are known to yield ketone III upon reaction with sulfuric acid.[7] Kascheras[9] has further demonstrated that upon reaction with 50% $H_2SO_4$ at 160° XI gives ketone III and IX gives a mixture of aldehyde II and III. It is indeed possible that IX and XI are the source of ketone III from XVIII (see p. 52) and arise through cation LI (see p. 53). Such a sequence was proposed by Kascheras[9] (Mechanism III, p. 55).

When 3-methyl-3-buten-1-ol (XLIX) was reacted with 50% $D_2SO_4$ at 160°,[9] the ketone III product was shown to consist of mainly the $d_{10}$ species (Table II, p. 51). The ketone product from 1-methylcyclobutanol (XLVII), under the same reaction conditions, was also mainly the $d_{10}$ species.[9] When XVIII and XLVII were recovered from the above reaction of XVIII with 50% $D_2SO_4$ neither product showed deuterium incorporation.[9] Extensive deuterium incorporation through interconverting protonated cyclopropanes[11] is thus precluded. These results are consistent with the reported tritiated sulfuric acid (51%) solvolysis of cyclopropane[12] in which no more than one tritium atom was incorporated in the product.

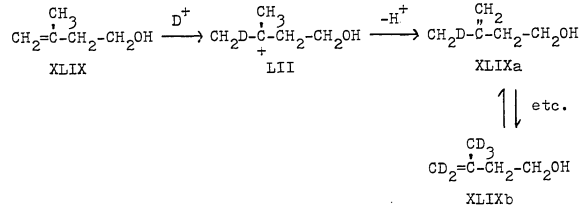
Allylic alcohols IX and XI have also been reacted with 50% $D_2SO_4$ at 160° (see Table II, p. 51).[9] In both cases, the ketone III product consisted of mainly the $d_5$ species. With reference to Mechanism IV, p. 58, extensive deuterium exchange in the reaction of XVIII to form ketone III-$d_{10}$ must take place between XLIX and cation LIa.

Mechanism III: Formation of 3-Methyl-2-butanone (III) from 1-Methylcyclopropylcarbinol (XVIII).



The source of the extensive deuterium exchange may involve an equilibrium between 3-methyl-3-buten-1-ol (XLIX) and its protonated species (LII) (see Scheme X) which would

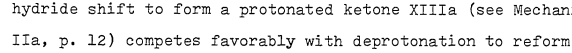
Scheme X: Reversible Deuteration of 3-Methyl-3-buten-1-ol (XLIX).




XLIX LII XLIXa XLIXb

lead to extensively deuterated alcohol XLIXb. A reversible protonation of the double bond in XLIX would not be analogous to that in Scheme III, p. 10, (XIa $\rightleftarrows$ XIIa), in which a 1,2-hydride shift to form a protonated ketone XIIIa (see Mechanism IIa, p. 12) competes favorably with deprotonation to reform XIa. In the case of LII no protonated carbonyl compound can result from a single 1,2-hydride shift and deprotonation to reform XLIX should be more competitive.

When XLIX was reacted with 5% sulfuric acid a 50% yield of 3-methyl-1,3-butanediol was obtained,[9] indicating, a



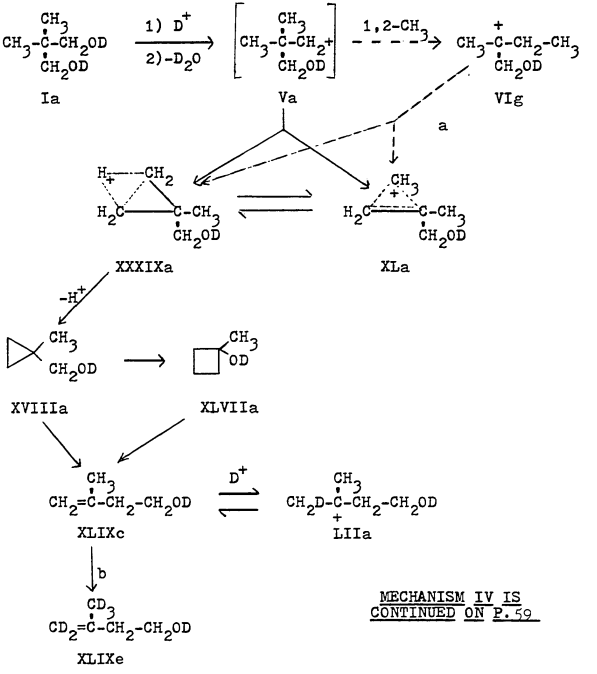

XLIX LIII

preference for reaction at the double bond, at least under

dilute acid conditions.

The proposed pathway, involving a cyclopropane intermediate, for the extensive deuterium incorporation in ketone III from the dehydration-rearrangement of diol Ia is shown in Mechanism IV, p. 58. Primary carbonium ions are bracketed and probably do not have any separate existence. Edge and corner protonated cyclopropanes XXXIXa and XLa, respectively, are depicted as forming both from Ia directly (solid arrows) and through the intermediacy of cation VIg (broken arrows) (see p. 52). Exchange between XLIX and LII results in deuteration of precisely those positions in XLIX which ultimately become the unexchangeable positions of ketone III according to Mechanism II, p. 7.

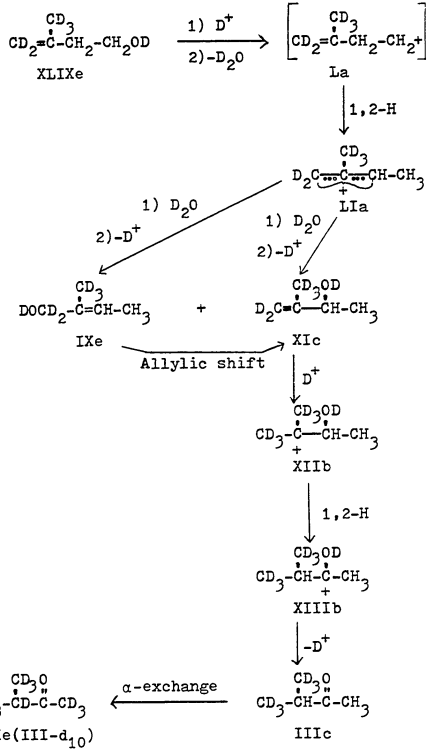
Mechanism IV: Formation of 3-Methyl-2-butanone (III-$d_{10}$) from the $D_2SO_4$-Catalyzed Dehydration-Rearrangement of 2,2-Dimethyl-1,3-propanediol-$(OD)_2$ (Ia) through 1-Methylcyclopropylcarbinol (XLIX).




MECHANISM IV IS CONTINUED ON P. 59

[a]Broken lines indicate XXXIXa and XLa formation from Ia through intermediate VIg.
[b]See Scheme X, p. 56.

Mechanism IV: continued.

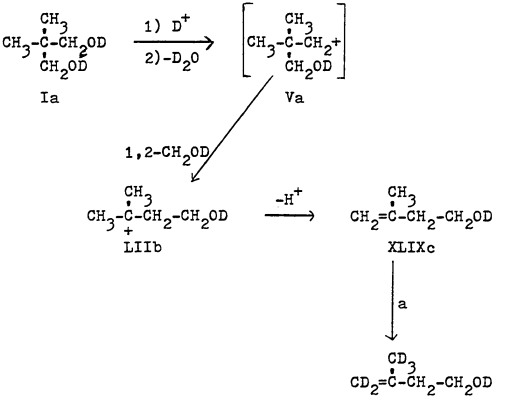


B) Methylol Shift Pathway

It is possible to consider 3-methyl-3-buten-1-ol (XLIX) as an intermediate in the formation of ketone III from diol I without postulating the intervention of a cyclopropyl precursor. In Mechanism V, p. 61, LIIb results from a 1,2-methylol ($-CH_2OD$) shift and, in turn, forms XLIXc upon deprotonation. Extensively deuterated XLIXe may be formed from XLIXc through the reactions of Scheme X, p. 56. Ketone III-$d_{10}$ could then form from XLIXe through Mechanism IV, p. 59.

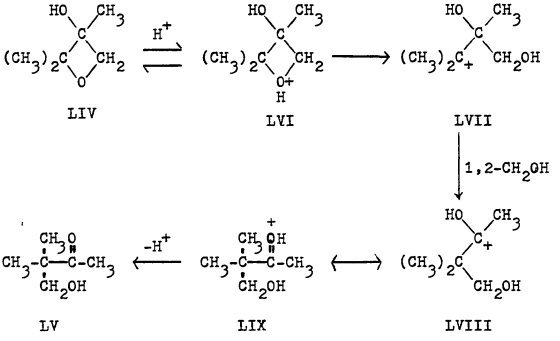
A small but growing number of examples are known in which electron-withdrawing substitiuents undergo intramolecular 1,2-shifts of the Wagner-Meerwein type.[22,23] Carbomethoxy groups have been reported to undergo 1,2-shifts with their electrons to a cationic center.[22] Kagan[24] has suggested a rearrangement sequence (Scheme XI, p. 62) which includes a 1,2-methylol shift in the acid-catalyzed conversion of 2,2,3-trimethyl-3-oxetanol (LIV) into 3-methyl-3-hydroxymethyl-2-butanone (LV). It is of interest that in LVII (Scheme XI, p. 62) a methylol ($-CH_2OH$) group migrates in preference to a methyl group.

Mechanism V: Formation of Deuterated 3-Methyl-3-buten-1-ol (XLIXe) from 2,2-Dimethyl-1,3-propanediol-$(OD)_2$ (Ia).




[a]See Scheme X, p. 56.

Scheme XI: A 1,2-Methylol Shift in the Formation of 3-Methyl-3-hydroxymethyl-2-butanone (LV).



C) Labeling Experiments

Isotopic labeling techniques have shown that a high degree of methylene group rearrangement accompanies solvolysis when cyclopropylcarbinyl (LX), cyclobutyl (LXI) and allylcarbinyl (LXII) derivatives interconvert.[25,26,27,28]

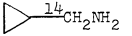
LX

LXI



LXII

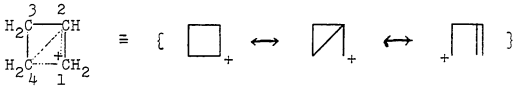
Roberts[29] found extensive but not complete methylene group scrambling during the nitrous acid deamination of cyclopropylcarbinyl-2-$^{14}$C-amine (LXIII). Similar results were observed by Schleyer[21] during the solvolysis of cyclopropylcarbinyl-1,1',1'-trans-2,3,3-$d_6$ methanesulfonate (LXIV).



LXIII

LXIV

Roberts and coworkers suggested that these interconversions proceed via a rapidly equilibrating set of non-classical bicyclobutonium ions.[29] A bicyclobutonium ion (LXV) is considered to be a resonance hybrid of the canonical structures LXV a ↔ c with geometry resembling that of

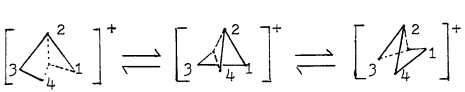


LXV LXVa LXVb LXVc

cyclobutane. For substituted cyclopropylcarbinyl systems, a set of equilibrating "symmetrical homoallylic" or "bisected" cyclopropylcarbinyl cations have been proposed to account for the interconversions.[30,31] A "bisected" cation (LXVI) is

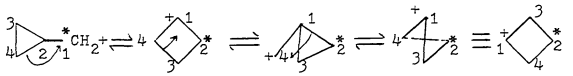
LXVI LXVIa LXVIb LXVIc LXVId

considered to be a resonance hybrid of canonical structures LXVIa-d. More recently, Olah[32] proposed a set of equilibrating structures containing three-center bonds (LXVIIa-c) to



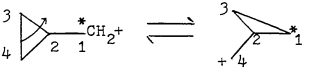
LXVIIa LXVIIb LXVIIc

explain these interconversions. We may consider scrambling in cyclopropylcarbinyl derivatives (LX) to occur either through cyclopropylcarbinyl (LXVIII)-cyclobutyl (LXIX) ion



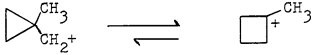
LXVIIIa LXIXa LXVIIIb LXIXb LXIXb

interconversions or through direct interconversions of cyclopropylcarbinyl (LXVIII) ions.



LXVIIIa LXVIIIc

Roberts has considered the interconversion of the 1-methylcyclopropylcarbinyl (LXX), 1-methylcyclobutyl (LXXI) and 3-methylallylcarbinyl (LXXII) cations. A minor contribution from equilibrating nonclassical cations was required to satisfactorily account for the labeling pattern in the 1-methylcyclobutanol (XLVII) product from the nitrous acid deamination of 1-methylcyclopropylcarbinyl-$\alpha$-$^{14}$C-amine (XLV-$^{14}$C).[20] Saunders has proposed that an equilibrium favoring the 1-methylcyclobutyl cation (LXXI) best describes the 1-methylcyclopropylcarbinyl cation (LXX).[33]

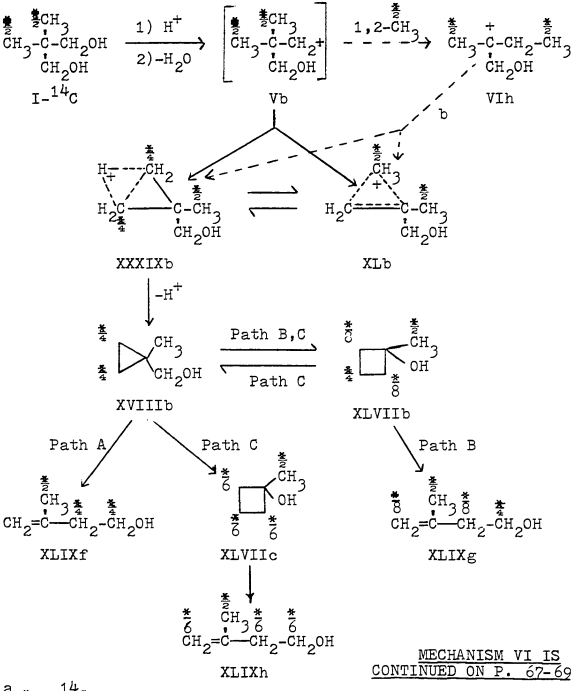


LXX LXXI

The recovery of non-deuterated XVIII and XLVII products from the reaction of XVIII with 50% $D_2SO_4$ (see p. 54) indicates that extensive exchange does not take place in the cyclopropyl or cyclobutyl structures.[9] There is little evidence for equilibrating nonclassical structures in the 1-methylcyclopropylcarbinyl system. Neither equilibrating protonated cyclopropanes nor other nonclassical cations, therefore, can be invoked to explain the carbon-14 distribution in 3-methyl-2-butanone (III) from the sulfuric acid-catalyzed dehydration-rearrangement of 2,2-(dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) (see p. 43).

Mechanism VI, p. 66, shows that in the dehydration-rearrangement of I-$^{14}$C the intermediacy of 1-methylcyclopropylcarbinol (XVIIIb) would, by virtue of its symmetry, predict

Mechanism VI: Formation of 3-Methyl-2-butanone (III) from the Sulfuric Acid-Catalyzed Dehydration-Rearrangement of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) through 1-Methylcyclopropylcarbinol (XVIII).[a]

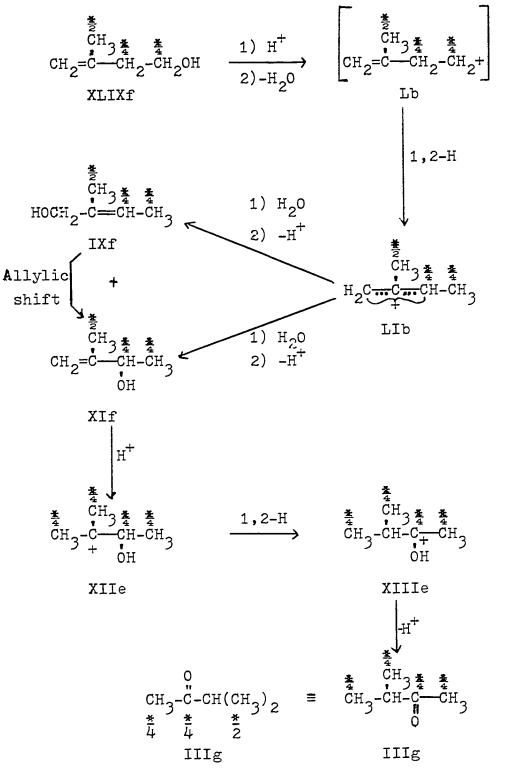



MECHANISM VI IS CONTINUED ON P. 67-69

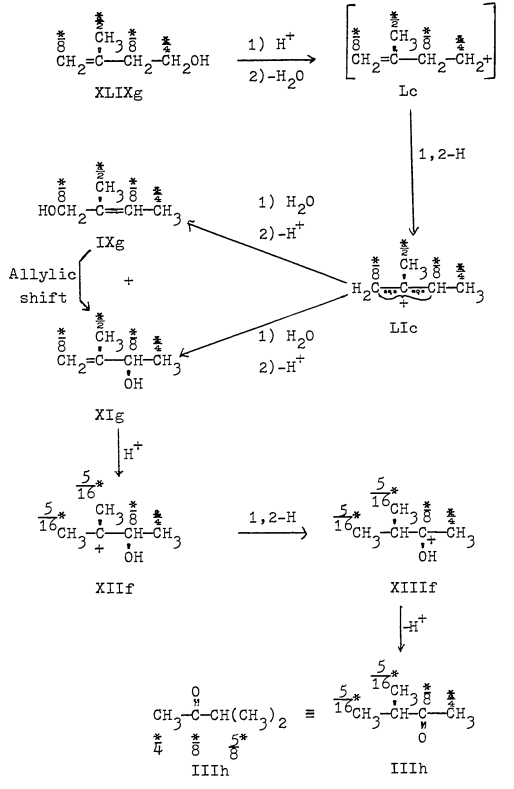
[a] * = $^{14}$C label.

[b] Broken lines indicate XXXIXb and XLb formation from I-$^{14}$C through intermediate VIh.

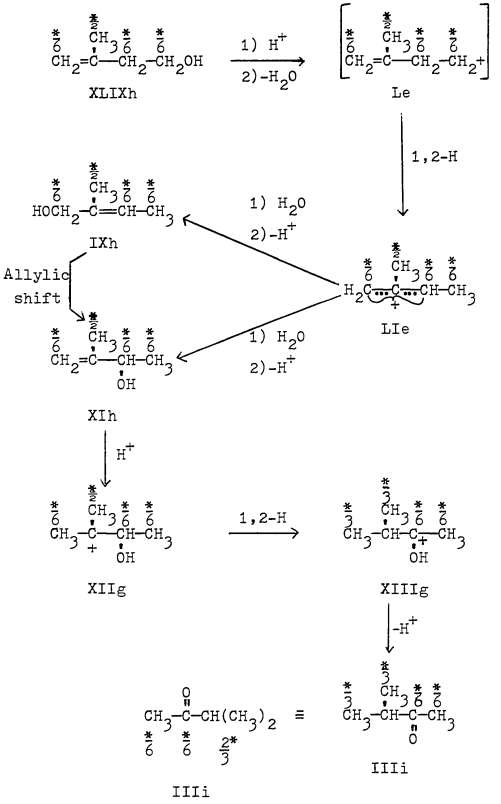
Mechanism VI; Path A continued.



Mechanism VI; Path B continued.



Mechanism VI; Path C continued.



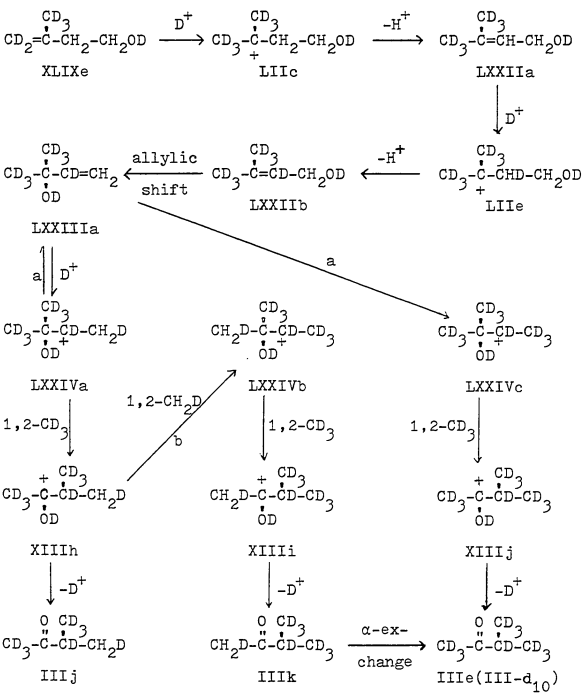
some methylene group equilibration and lead to carbon-14 at the C-2 position of ketone III. The allylic pathway (p. 47) predicts the absence of carbon-14 at C-2. The 1-methylcyclopropylcarbinyl cation (LXXa) of XVIIIb (see Mechanism VI, p. 66) may 1) ring-open to the 3-methylallylcarbinyl cation (Lb) of XLIXf directly (Path A); 2) form Lc through the irreversible formation of the 1-methylcyclobutyl cation (XLVIIb) (Path B) or 3) form Le after complete equilibration with XLVIIc (Path C).

Mechanism IV, p. 58, does not represent the only possible pathway by which XLIXe could form completely deuterated ketone-$d_{10}$. Another pathway is shown in Mechanism VII, p. 71. In support of this mechanism as a possible pathway in our work, 3-methyl-2-buten-1-ol (LXXII), upon reaction with 50% $D_2SO_4$ at 160°, has been shown to give a low yield of ketone III and aldehyde II, in a 9 : 1 ratio.[9] The incorporation of six deuterium atoms in LXXIIa (Mechanism VII, p. 71) can result from the reversal of XLIX → LII (see Scheme X, p. 56). It should be noted that Mechanism VII cannot account for ketone III-$d_{10}$ unless either LXXIV → XIII or LXXIII → LXXIV are reversible. The reversal of LXXIV → XIII could lead to LXXIVb which would lead to IIIk, which after

$$\underset{\text{LXXIVb}}{CH_2D\text{-}\overset{CD_3}{\overset{|}{\overset{+}{C}}}\text{-}\overset{|}{C}D\text{-}CD_3} \xrightarrow{1,2\text{-}CD_3} \underset{\text{XIIIi}}{CH_2D\text{-}\overset{+}{\overset{|}{C}}\text{-}\overset{CD_3}{\overset{|}{C}}D\text{-}CD_3} \xrightarrow{-D^+} \underset{\text{IIIk}}{CH_2D\text{-}\overset{O}{\overset{\|}{C}}\text{-}CD(CD_3)_2}$$

α-exchange, would form III-$d_{10}$. The reversal of LXXIV → XIII in Mechanism VII, p. 71, is not analogous to the reversal of

Mechanism VII: Formation of 3-Methyl-2-butanone (III-$d_{10}$) from Deuterated 3-Methyl-3-buten-1-ol (XLIXe) through 3-Methyl-2-buten-1-ol (LXXII).




[a]Reversal of LXXIII → LXXIV ((LXXIII ⇌ LXXIV) → LXXIVc).
[b]Reversal of LXXIV → XIII (LXXIVa → XIIIh → LXXIVb).

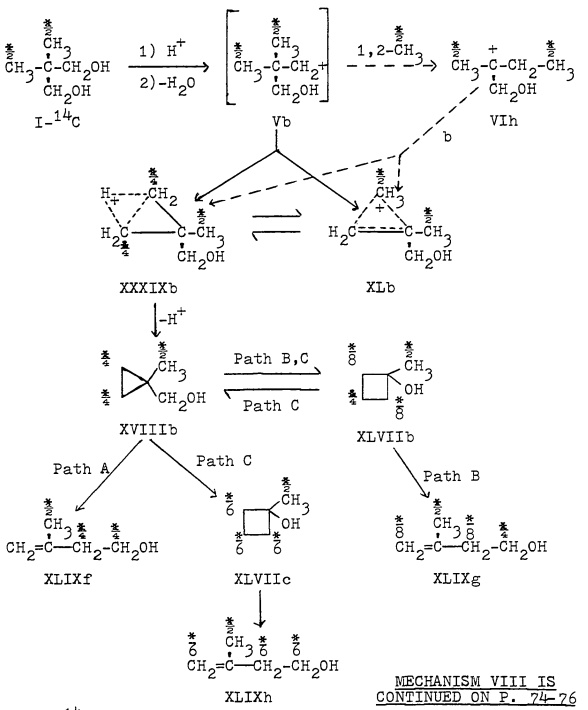
XI → XII in Scheme III, p. 10. Here a 1,2-methyl shift is required to form a protonated carbonyl compound and deprotonation to reform LXXIII should be more important.[34,35,36] Mechanism VIII, p. 73, shows the predicted carbon-14 distribution in ketone III from I-$^{14}$C that would result from a pathway of the type shown in Mechanism VII, p. 71, which involves LXXII as an intermediate. As in Mechanism VI, p. 66, the relation between XVIII and XLVII before the formation of XLIX affects the carbon-14 label distribution, in this case, in the extent of label at the C-3 position of ketone III.

Mechanism IX, p. 77 shows the predicted carbon-14 distribution in ketone III from diol I-$^{14}$C, by way of the 1,2-methylol shift pathway (Mechanism V, p. 61). All activity would be expected at the C-4 position of III. This pathway cannot account for the appearance of activity at the C-2 and C-3 positions (Table XIII, p. 80).

The possibility was considered that the combination of a 1,2-methylol shift and the intermediacy of 3-methyl-2-buten-1-ol (LXXIII) might be able to explain our results (Table XIII, p. 80) and thus obviate the necessity of invoking a cyclopropyl intermediate. Mechanism X, p. 78, shows that such a combination leads only to carbon-14 at the C-1 and C-4 positions of ketone III in the manner of mechanism I-$^{14}$C, p. 48 (Table XIII, p. 80).

Only mechanisms involving a cyclopropane intermediate predict carbon-14 labeling at the C-2 and C-3 positions of ketone III, as was found experimentally (Table XIII, p. 80).

Mechanism VIII: Formation of 3-Methyl-2-butanone (III) from the Sulfuric Acid-Catalyzed Dehydration-Rearrangement of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) through 1-Methylcyclopropylcarbinol (XVIIIb) and 3-Methyl-2-buten-1-ol (LXXII).[a]

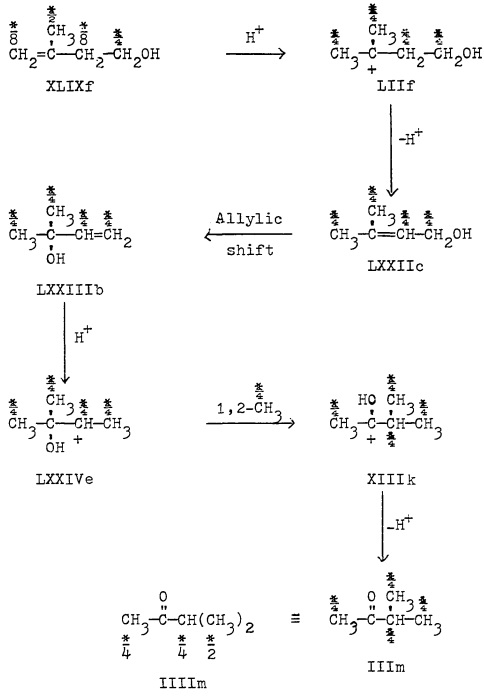



MECHANISM VIII IS CONTINUED ON P. 74-76

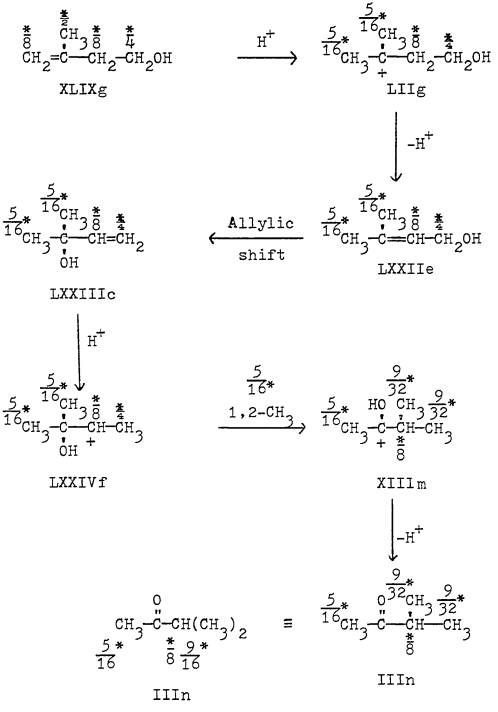
[a] * = $^{14}$C label.

[b] Broken lines indicate XXXIXb and XLb formation from I-$^{14}$C through intermediate VIh.

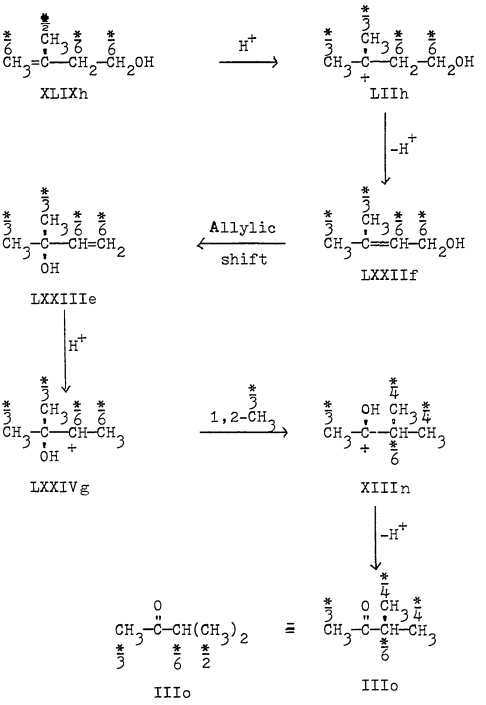
Mechanism VIII; Path A continued.



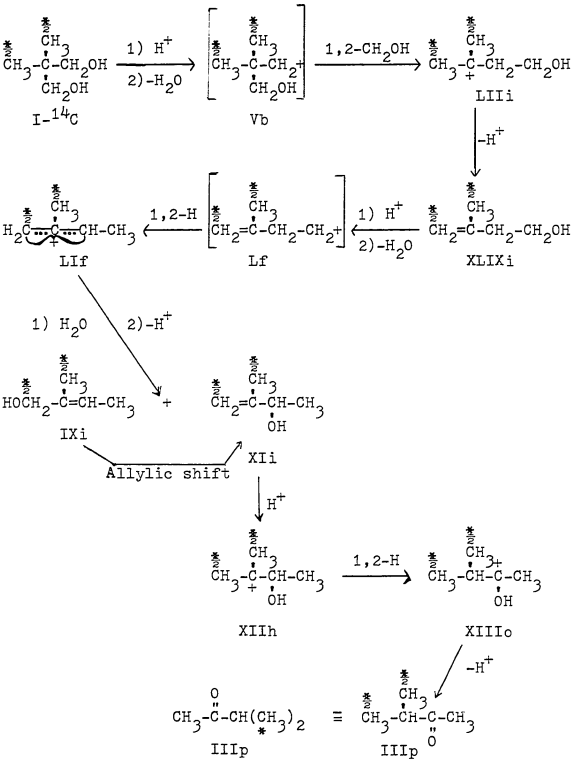
Mechanism VIII; Path B continued.



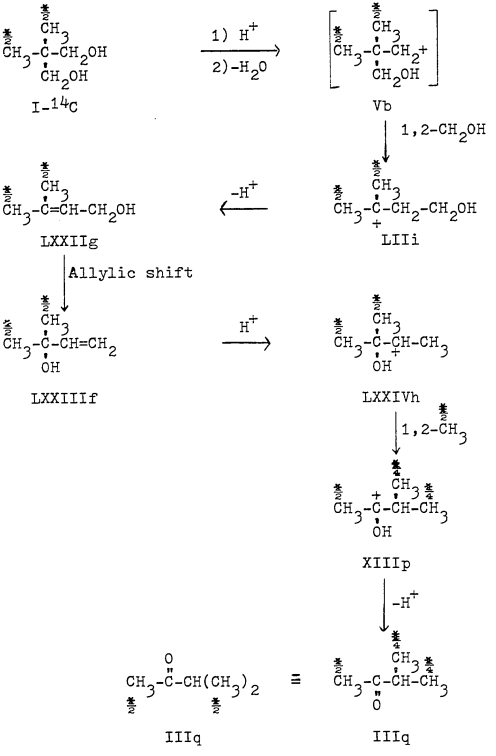
Mechanism VIII; Path C continued.



Mechanism IX: Formation of 3-Methyl-2-butanone (III) from the Sulfuric Acid-Catalyzed Dehydration-Rearrangement of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) through a 1,2-Methylol Shift.



Mechanism X: Formation of 3-Methyl-2-butanone (III) from the Sulfuric Acid-Catalyzed Dehydration-Rearrangement of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) through a 1,2-Methylol Shift and Intermediate LXXII.



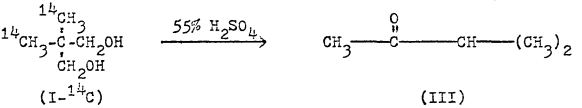
IV Extent of Cyclopropane Intermediate Pathways

Carbon-14 at the C-2 and C-3 positions of 3-methyl-2-butanone (III)[b1] is considered to arise from Mechanism VI, (p. 66) and Mechanism VIII (p. 73), respectively. Both mechanisms include 1-methylcylcopropylcarbinol (XVIII) as an intermediate. The extent to which these mechanisms contribute to the overall formation of ketone III in the reaction of diol I with sulfuric acid was considered.

Based upon the average values of carbon-14 label in the C-2 and C-3 positions of ketone III (Table XIII, p. 80), maximum and minimum contributions from Mechanisms VI and VIII can be calculated. The maximum contribution from Mechanism VI is calculated by dividing 3.8, the average observed percentage of carbon-14 at C-2, by 12.5, the predicted percentage of carbon-14 at C-2 assuming all ketone III is formed through the irreversible formation of XLVII from XVIII (Path B, Mechanism VI, p. 66). This maximum value is 30.4%. The minimum contribution from Mechanism VI is calculated by dividing the same 3.8 by 25.0, the predicted percentage assuming all ketone III is formed through the direct ring-opening of XVIII (Path A). This value is 15.2%.

By similar calculations based on the average observed percentage of carbon-14 at C-3 (0.9), the maximum (Path B) and minimum (Path A) contributions from Mechanism VIII, p. 73, are 7.2% and 3.6%, respectively. These results are summarized in Table XIV, p. 82. The total contribution of

Table XIII: Expected Carbon-14 Distribution in 3-Methyl-2-butanone (III) from the Sulfuric Acid-Catalyzed Dehydration-Rearrangement of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) as a Function of Mechanism




(I-$^{14}$C) (III)

| Mechanism | {C-1} | {C-2} | {C-3} | {C-4} |
|---|---|---|---|---|
| (Experimental Values[a]) | 43.7± 0.7 | 3.8± 0.7 | 0.9± 0.2 | 51.6± 0.3 |
| Mechanism I-$^{14}$C(p. 47) | 50.0 | | | 50.0 |
| Mechanism VI(Path A)(p. 67) | 25.0 | 25.0 | | 50.0 |
| (Path B)(p. 68) | 25.0 | 12.5 | | 62.5 |
| (Path C)(p. 69) | 16.67 | 16.67 | | 66.67 |
| Mechanism VIII(Path A)(p. 74) | 25.0 | | 25.0 | 50.0 |
| (Path B)(p. 75) | 31.25 | | 12.5 | 56.25 |
| (Path C)(p. 76) | 33.33 | | 16.67 | 50.0 |
| Mechanism IX(p. 77) | | | | 100.0 |
| Mechanism X(p. 78) | 50.0 | | | 50.0 |

[a]See Table XII, p. 32.

cyclopropane intermediate pathways in the formation of ketone III, calculated in this manner, has a maximum value of 37.6% if Path B is followed and a minimum value of 18.8% if Path A is followed.

Included in Table XIV, p. 82, are the calculated contributions from Mechanisms VI and VIII assuming that all ketone III is formed after complete equilibrium is established between intermediates XVIII and XLVII (Path C, Mechanism VI, p. 66). The calculated contributions from Mechanisms VI and VIII, assuming Path C, are intermediate between those calculated for Paths A and B. Thus, a contribution from Path C is considered indistinguishable from a combined contribution from Paths A and B. As noted previously (p. 65), equilibrating nonclassical ions do not play more than a minor role in the 1-methylcyclopropylcarbinyl/1-methylcyclobutyl/3-methylallylcarbinyl system. Path C will thus not be considered further in calculations to determine the extent of involvement of cyclopropane intermediate pathways.

In an attempt to reproduce, through calculations, the observed carbon-14 distribution in ketone III, combinations of Mechanism VI, p. 66, Mechanism VIII, p. 73, and Mechanism I, p. 3, were considered. Table XV, p. 83, shows the expected carbon-14 distribution in ketone III, formed from various combinations of pathways. Combination B1 represents the maximum amounts (p. 79) of Mechanisms VI and VIII which would lead to the observed labeling at C-2 and C-3. Combination A1 represents the minimum amounts (p. 79) of Mechanisms VI

Table XIV: Calculated Contributions from the Various Paths of Mechanism VI and Mechanism VIII in the Formation of 3-Methyl-2-butanone (III).

| | Contribution | | |
|---|---|---|---|
| | Path A | Path B | Path C |
| Mechanism VI (C-2) | 15.2% | 30.4% | 22.8% |
| Mechanism VIII (C-3) | 3.6% | 7.2% | 5.4% |
| Total Cyclopropane Intermediate Patway Contribution | 18.8% | 37.6% | 28.8% |

Table XV: Expected Carbon-14 Distribution in 3-Methyl-2-butanone (III) Formed from Various Combinations of Mechanisms.[a]

| Combination | Composition | Carbon-14 Distribution C-1 | C-2 | C-3 | C-4 |
|---|---|---|---|---|---|
| (Experimental Values) | | 43.7± 0.7 | 3.8± 0.7 | 0.9± 0.2 | 51.6± 0.3 |
| B1 | 30.4%[Mechanism VI(Path B)] + 7.2%[Mechanism VIII(Path B)] + 62.4% Mechanism I | 41.1 | 3.8 | 0.9 | 54.2 |
| A1 | 15.2%[Mechanism VI(Path A)] + 3.6%[Mechanism VIII(Path A)] + 81.2% Mechanism I | 45.3 | 3.8 | 0.9 | 50.0 |
| Mixture I (45% B1 + 55% A1) | | 43.4 | 3.8 | 0.9 | 51.9 |
| B2 | 36.0%[Mechanism VI(Path B)] + 8.8%[Mechanism VIII(Path B)] + 55.2% Mechanism I | 39.4 | 4.5 | 1.1 | 55.0 |
| A2 | 18.0%[Mechanism VI(Path A)] + 4.4%[Mechanism VIII(Path A)] + 77.6% Mechanism I | 44.4 | 4.5 | 1.1 | 50.0 |
| Mixture II (40% B2 + 60% A2) | | 42.4 | 4.5 | 1.1 | 52.0 |

[a]See Table XIII, p. 80, for carbon-14 distribution in ketone III due to individual mechanisms.

and VIII which would lead to the observed labeling at the C-2 and C-3 positions. Both, however, predict values somewhat different from those observed for Carbon-14 at C-1 and C-4. Mixture I (45% B1 and 55% A1) is consistent with, (within experimental error), the observed values for all positions of ketone III.

As shown in Table XVI, p. 85, Mixture I calls for the total contribution of cyclopropane intermediate pathways in the formation of ketone III to be 27.3%.

As shown in Table IV, p. 23, 51%±2% of ketone III from the reaction of diol Ia with 55% $D_2SO_4$ is obtained as $d_9$ or $d_{10}$ species. Approximately 6% (the amount of II-$d_4$ or $d_5$ from Table III, p. 22) of III-$d_9$,$d_{10}$ that could be attributed to Scheme II, p. 10 or Scheme III, p. 10 (see p. 13). Therefore, 45%±2% can be considered as the amount of ketone III-$d_9$,$d_{10}$ formed through a pathway other than the allylic shift pathway (Mechanism II, p. 7).

Every cyclopropane pathway includes, as an intermediate, 1-methylcylopropylcarbinol (XVIII) which has been shown by Kascheras[9] to give 87.5% ($d_9$ + $d_{10}$) ketone III (see Table II, p. 51). Ketone III from diol Ia showed considerably more deuteration under our conditions (55% $D_2SO_4$ at 150°), than ketone III from diol I under the conditions (50% $D_2SO_4$ at 160°) of Kascheras[9] (see Table IV, p. 23). Under the present conditions then, XVIII would be expected to lead to essentially completely deuterated ketone III. All ketone III formed through a cyclopropane intermediate pathway, therefore, is expected to be $d_9$ or $d_{10}$ species. If all the ketone III-

Table XVI: Total Contribution of Cyclopropane Intermediate Pathways to the Formation of 3-Methyl-2-butanone (III) from the Sulfuric Acid-Catalyzed Dehydration-Rearrangement of 2, 2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) Predicted by Mixture I.[a]

| Mixture I | | | Cyclopropane Intermediate Pathway Contribution |
|---|---|---|---|
| 45% Combination B1 | | | |
| 0.45 x 30.4% | Mechanism VI(Path B) | = 13.7% | |
| 0.45 x 7.2% | Mechanism VIII(Path B) | = 3.2% | |
| 0.45 x 37.6% | Total Paths B | | 16.9% |
| 55% Combination A1 | | | |
| 0.55 x 15.2% | Mechanism VI(Path A) | = 8.4% | |
| 0.55 x 3.6% | Mechanism VIII(Path A) | = 2.0% | |
| 0.55 x 18.8% | Total Paths A | | 10.4% |
| | Total Mechanism VI | 22.1% | |
| | Total Mechanism VIII | 5.2% | |
| | Total Overall Contribution | | 27.3% |

[a] [45%(Combination B1) + 55%(Combination A1)](see Table XV, p. 83, and p. 81.

$d_9$,$d_{10}$ from a pathway other than Mechanism I (see above) were formed through a cyclopropane intermediate pathway, the deuterium study results indicate a contribution by such pathways of 43-49%.

The observed carbon-14 distribution in ketone III is consistent with a maximum of 27.3% contribution from cyclopropane intermediate pathways (Table XVI, p. 85). Additional calculations were performed to determine if other combinations of Mechanisms I, VI and VIII would lead to a greater involvement of cyclopropane intermediate pathways while still giving the observed carbon-14 distribution. Table XV, p. 83, shows that a mixture of 40% combination B2 and 60% combination A2 (Mixture II) predicts a distribution of carbon-14 in ketone III very close to the observed distribution. Table XVII, p. 87, shows that Mixture II calls for a 31.3% contribution from cyclopropane intermediate pathways to the formation of ketone III. Although other mixtures of combinations of mechanisms could be conceived, 31-32% appears to be the maximum contribution of cyclopropane pathways to the formation of ketone III, that would be consistent with the observed carbon-14 distribution.

Both carbon-14 and deuterium labeling studies indicate that in the sulfuric acid-catalyzed dehydration-rearrangement of diol I (Ia), ketone III is formed through both the allylic shift pathway (Mechanism I, p. 3) and cyclopropane intermediate pathways (Mechanism VI and VIII, p. 66 and 73, respectively). The two studies differ, however, in their predictions

Table XVII: Total Contribution of Cyclopropane Intermediate Pathways to the Formation of 3-Methyl-2-butanone (III) from the Sulfuric Acid-Catalyzed Dehydration-Rearrangement of 2, 2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) predicted by Mixture II.[a]

| Mixture II | | | Cyclopropane Intermediate Pathway Contribution |
|---|---|---|---|
| 40% Combination B2 | | | |
| 0.40 x 36.0% Mechanism VI(Path B) | = 14.4% | | |
| 0.40 x 8.8% Mechanism VIII(Path B) | = | 3.5% | |
| 0.40 x 44.8% Total Paths B | | | 17.9% |
| 60% Combination A2 | | | |
| 0.60 x 18.0% Mechanism VI(Path A) | = 10.8% | | |
| 0.60 x 4.4% Mechanism VIII(Path A) | = | 2.6% | |
| 0.60 x 22.4% Total Paths A | | | 13.4% |
| Total Mechanism VI | 25.2% | | |
| Total Mechanism VIII | | 5.2% | |
| Total Overall Contribution | | | 31.3% |

[a][40%(Combination B2) + 60%(Combination A2)](see Table XV, p. 83, and p. 86.

of the extent to which these pathways contribute to ketone III formation. The deuteration studies indicate 43-49% cyclopropyl intermediate pathway while the carbon-14 labeling results indicate 27-32%. The difference between these results is 11-22%.[a]

An attempt to rationalize the difference between these two types of studies will now be made in the context of the mechanisms already presented.

The reaction media were 55% v/v (70.2% w/w) $H_2SO_4$ in the carbon-14 studies and 55% v/v (70.2% w/w) $D_2SO_4$ in the deuterium studies. The Hammett acidity functions, Ho and Do,[37] have been shown to be equal over our acidity range,[38,39] and the dielectric constants for $H_2O$ and $D_2O$ are reported to be very similar.[40] $D_2O$, however, has been reported to be a weaker base than $H_2O$.[41,42] The fact that most acid-catalyzed reactions proceed at a higher rate in $D_2O$ than in $H_2O$ has been attributed to this fact.[33]

The reactions of substrates containing hydroxyl groups as the basic functions usually exhibit specific hydrogen ion catalysis as shown in Scheme XII (J=H or D).[43] The first

Scheme XII: Mechanism of Acid Catalysis.

$$S + J^+.\text{solvent} \underset{\text{fast}}{\rightleftharpoons} SJ^+ + \text{solvent} \quad (A)$$

$$SJ^+ (+X) + \text{solvent} \xrightarrow[\text{slow}]{} \text{products} + J^+.\text{solvent} \quad (B)$$

---

[a] 43 - 49% predicted by deuterium studies
-27 - 32% predicted by carbon-14 studies
11 - 22% (min. 11% = 43% - 32%) (max. 22% = 49% - 27%)

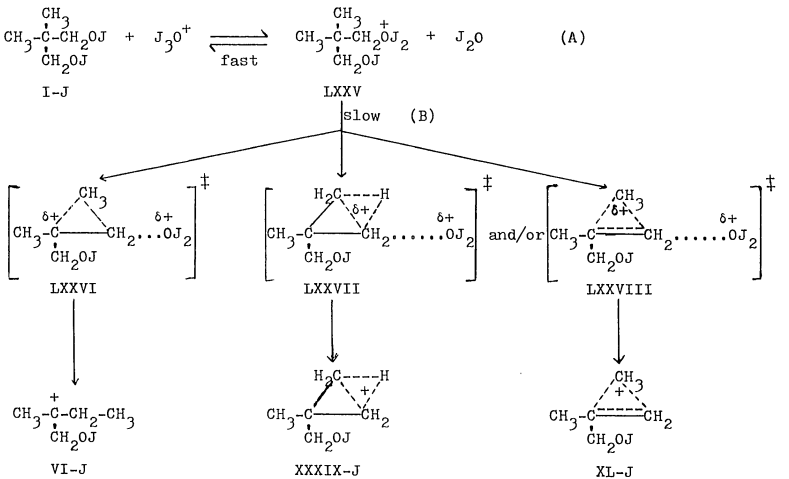
step (A) is the rapid reversible formation of the conjugate acid of substrate S. In the second step (or sequence of steps), (B), the slow step, which may or may not be unimolecular, is assumed here to not involve a proton transfer. The conjugate acid $SH^+$ has been shown to be stronger than $SD^+$ by a factor of 2.5 - 3.5.[34] Since the rate of the reaction is directly proportional to the concentration of $SJ^+$, the ratio of the observed rate constants $k_{D_2O}/k_{H_2O}$ should be greater than one. For reactions which are thought to proceed by the path shown in Scheme XII, p. 88, $k_{D_2O}/k_{H_2O}$ has been found to be in the range 1.5 - 2.8.[44]

If two or more products are formed in Scheme XII, p. 88, the product-ratio will be determined by step (B). If one product is formed, but from two or more divergent pathways, the ratio of pathways will also be determined by step (B). In the acid-catalyzed dehydration of diol I, ketone III is formed from both the allylic shift and cyclopropane intermediate pathways. It is possible that in changing the reaction system from $H_2SO_4/H_2O$ to $D_2SO_4/D_2O$, the ratio of pathways followed in the formation of ketone III is affected.

In Mechanism IV, p. 58, cyclopropane pathway intermediates XXXIXa and XLa are depicted as forming from diol Ia with or without the intermediacy of cation VIg (see p. 52). The allylic shift and cyclopropane intermediate pathways can thus be considered to have two possible points of divergence, as shown in Scheme XIII, p. 90 and Scheme XIV, p. 94.

Scheme XIII, p. 90, shows the first two steps of the

Scheme XIII: The First Two Steps in the Mechanism of the Acid-Catalyzed Dehydration-Rearrangement of 2,2-Dimethyl-1,3-propanediol-$(OJ)_2$ (I-J).



acid-catalyzed dehydration of diol I-J. It is assumed here that the protonated cyclopropane intermediates of Mechanism IV, p. 58, are formed without the intermediacy of cation VI. In the rate-determining sequence (B), competition exists between the unimolecular transformation of LXXV into intermediates VI-J and either XXXIX-J or XL-J (or both). The transition states in their formation are depicted as LXXVI, LXXVII and LXXVIII, respectively. Cation VI gives rise to ketone III through the allylic shift pathway (Mechanism I, p. 3) and intermediates XXXIX and XL give rise to ketone III through cyclopropane pathways (see Scheme VII, p. 50 and Mechanism III, p. 55). Greater stabilization of LXXVII and LXXVIII relative to LXXVI in changing the reaction medium from $H_2SO_4/H_2O$ to $D_2SO_4/D_2O$ would result in a greater contribution of cyclopropane pathways to ketone III formation.

Protonated cyclopropanes are intermediate in stability between primary and secondary carbonium ions.[45,46,47] Tertiary cation VI-J (Scheme XIII, p. 90) is expected, therefore, to be more stable than either XXXIX-J or XL-J. Since transition states and the products which they form are generally stabilized by the same factors, we should expect LXXV → LXXVI to be less endothermic than either LXXV → LXXVII or LXXV → LXXVIII. This is in agreement with both the deuterium and carbon-14 experiments which indicate that most of ketone III is formed through the allylic shift pathway (Mechanism I, p. 3), which includes cation VI as an intermediate.

Hammond's postulate[48] states that for a series of

similar reaction steps, the less endothermic a reaction step, the closer in structure will the transition state be to the starting state, and conversely, the more endothermic a reaction step, the closer in structure will the transitions state be to the product. If we assume that in Scheme XIII, p. 90, LXXV → VI-J and LXXV → XXXIX-J (or LXXV → XL-J) are similar steps (the starting states are the same), we would predict that LXXVII is closer in structure to XXXIX-J (and LXXVIII to XL-J) than LXXVI is to VI-J. Therefore, the leaving of $J_2O$ is depicted in LXXVII and LXXVIII as having progressed further than in LXXVI.

As mentioned previously, $D_2O$ is a weaker base than $H_2O$[41,42] and, therefore, $J_2O$ is expected to be a better leaving group in the $D_2SO_4/D_2O$ system. Since the leaving of $J_2O$ is more importent in LXXVII (and LXXVIII), these transition states are expected to be preferentially stabilized compared to LXXVI when the reaction system is changed from $H_2SO_4/H_2O$ to $D_2SO_4/D_2O$.

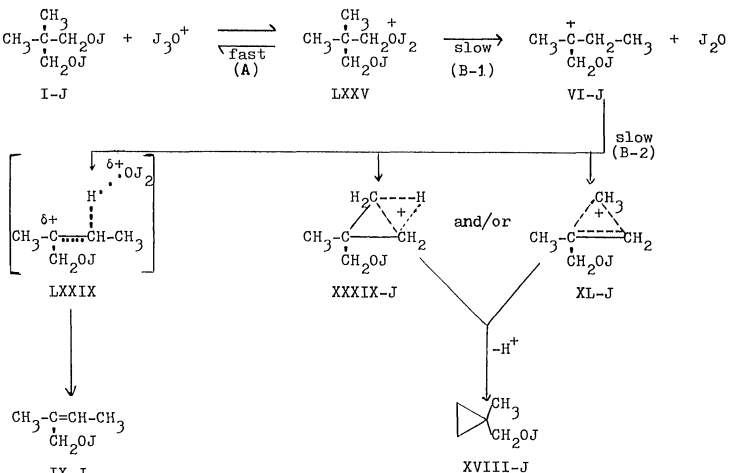
Solvent isotope effects may also play a role in the relative stabilities of transition states LXXVI, LXXVII and LXXVIII. No detailed studies of the properties of $D_2SO_4/D_2O$ mixture have been reported.[49] Both solvent systems ($H_2SO_4/H_2O$ and $D_2SO_4/D_2O$) are approximately two-thirds water by molar percent (70.2% acid by wt. = 69.8 molar % $H_2O$, 68.0 molar % $D_2O$). A transition state in which the insipient charge is more developed and more localized is expected to be preferentially solvated in $H_2O$. Because the leaving of

the $J_2O$ group has progressed further in transition states LXXVII and LXXVIII than in LXXVI (Scheme XIII, p. 90), it might be expected that more insipient charge would have developed in LXXVII and LXXVIII. On the other hand, the developing charge in LXXVII and LXXVIII, as depicted, would be expected to be less localized. A definite conclusion on the direction of the solvent isotope effect cannot, therefore, be made. However, leaving group considerations appear to indicate that transition states LXXVII and LXXVIII are stabilized relative to LXXVI when the reaction media is changed from $H_2SO_4/H_2O$ to $D_2SO_4/D_2O$. Thus, if protonated cyclopropane intermediates are formed according to Scheme XIII, p. 90, a larger contribution from cyclopropane pathways would be expected in the $D_2SO_4/D_2O$ reaction system. This is in agreement with our experiemental results.

In Mechanism IV, p. 58, cyclopropane pathway intermediates may also form from diol Ia through the intermediacy of Cation VIg. In Scheme XIV, p. 94, LXXV is formed from I-J in a fast pre-equilibrium step (A) which then, in turn, rearranges to VI-J in a slow step (B-1). Tertiary cation VI-J can then, in a second slow step (B-2), form IX-J through LXXIX or XVIII-J through XXXIX-J (and/or XL-J). Intermediate IX gives rise to ketone III through the allylic shift pathway and intermediate XVIII gives ketone III through cyclopropane pathways.

In (B-2) of Scheme XIV, p. 94, VI-J → LXXIX involves the transfer of a proton to the solvent while VI-J → XXXIX-J

Scheme XIV: Formation of 1-Methylcyclopropylcarbinol-(OJ) (XVIII-J) and 2-Methyl-2-buten-1-ol-(OJ) (IX-J) from 2,2-Dimethyl-1,3-propanediol-$(OJ)_2$ (I-J) through the Common Intermediacy of Cation VI-J.



(and/or XL-J) involves the reorganization of carbon-to-hydrogen bonds as the tertiary cation is transformed into a protonated cyclopropane. $H_2O$ is more basic than $D_2O$[41,42] and is thus better able to abstract a proton. Since proton abstraction is more important in VI-J → LXXIX than in VI-J → XXXIX-J (and/or VI-J), it is expected, that the former path should be preferentially stabilized when the reaction system is changed from $D_2SO_4/D_2O$ to $H_2SO_4/H_2O$. Conversely, in changing from $H_2SO_4/H_2O$ to $D_2SO_4/D_2O$ VI-J → XXXIX-J (and/or XL-J) should be preferentially stabilized and a higher contribution from cyclopropane pathways to ketone III formation would be expected. This is in accord with our experimental results.

In Mechanism IV, p. 58, cyclopropane pathway intermediates XXXIXc and XLc may form from diol Ia with and/or without the intermediary of cation VIg. In either case it is possible to account for the difference in the predicted cyclopropane pathway contribution to ketone III formation, on changing the reaction medium from $H_2SO_4/H_2O$ to $D_2SO_4/D_2O$ by basicity and solvation effects.

In changing the reaction media from $H_2SO_4/H_2O$ to $D_2SO_4/D_2O$, the effect on the relative stabilities of the transition states of the competing pathways in both Schemes XIII, p. 90 and Scheme XIV, p. 94, is expected to be small. The predicted cyclopropane pathway contribution to ketone III formation in the carbon-14 ($H_2SO_4/H_2O$) and deuterium ($D_2SO_4/D_2O$) studies differs by only 11-22% (see p. 88).

A relative change in $\Delta G^{\ddagger}$ ($G^{\ddagger}$ = free energy of activation) of only 0.088-0.18 Kcal./mole in the competing pathways of either scheme is sufficient to account for such a difference. Any attempt to rationalize the cause of such a small difference probably carries with it a large probability of being in error. The arguments presented in pages 88-95, should, perhaps, be taken with a small grain of salt. In addition, the yields of ketone III and aldehyde II from the acid-catalyzed dehydration-rearrangement of diol I were (43.8-55.4%) and (9.0-11.8%), respectively, (see p. 108 and 131). These yields were an improvement over previous studies[9] in which the combined yield of ketone III and aldehyde II was only 15%. There is a substantial amount of material from diol I not accounted for by volatile carbonyl product. Yvernault and Mazet[3] reported the formation of some non-distillable resins, as well as acetal IV (see p. 1), from the reaction of diol I with sulfuric acid. Kascheras[9] has reported some high molecular weight product from the sulfuric acid reaction of 3-methyl-3-buten-1-ol (XLIX), which is an intermediate in both cyclopropane pathways (Mechanisms VI and VIII, pp. 66 and 73, respectively). Changing solvent systems, from $H_2SO_4/H_2O$ to $D_2SO_4/D_2O$, might alter the relative amounts of resinous products formed in the cyclopropane and non-cyclopropane pathways and, thus, affect the ratio of volatile products formed through these pathways. This would make the observed results in the deuteration and carbon-14 studies not correspond to the real ratio of allylic

to cyclopropane pathways.

In conclusion, the results presented in this dissertation implicate a here-to-for unsuspected pathway, involving a cyclopropane intermediate in the acid-catalyzed rearrangement of 2,2-dimethyl-1,3-propanediol (I) to 3-methyl-2-butanone (III). Under our reaction conditions this pathway accounts for approximately 30% of the product.

## Experimental Section

Melting points were determined using a Thomas-Hoover apparatus, in open capillary tubes, and are corrected; boiling points are uncorrected. Mass spectra were determined using a Varian CH5 Mass Spectrometer at 70 ev with linear mass scan. Proton magnetic resonance spectra were determined using a Joel MH-100 spectrometer. Chemical shifts are expressed in ppm ($\delta$) downfield from internal tetramethylsilane ($\delta$=0). Gas liquid chromatography was performed using either a Varian 1860 chromatograph with flame ionization detection (Col. 1 and Col. 2) or a Varian A90-P chromatograph with thermal conductivity detection (Col. 3).

Column 1 Tris-(cyano-2-ethoxypropane) (TCEP) (10%) on 80/100 mesh varaport 30 in a 1/8" X 10' stainless steel column.

Column 2 Diethylene glycol adipate (DEGA) (10%) on 80/100 mesh varaport 30 in a 1/8" X 10' stainless steel column.

Column 3 TCEP (20%) on 70/80 mesh chromosorb P in a 1/4" X 20' stainless steel column.

Molar activities were determined using a Beckman LS-150 Liquid Scintillation System. Samples were counted in a modified Bray's Solution consisting of 60 g. of napthalene, 4 g. of 2,5-diphenyloxazole (PPO) and 0.2 g. of 1,4-bis[2-(5-phenyloxazolyl)] benzene (POPOP) dissolved in a mixture of 880 ml. of p-dioxane, 100 ml. of methanol and 20 ml. of ethylene glycol. All samples were corrected for quenching.

Whenever a reaction was run overnight or a radioactive compound was heated, two condensers in series were employed. One was cooled with circulating alcohol (in case of a water pressure drop) and the other with water (in case of electrical failure.

I Preparation of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C)

A) Synthesis of Ethyl 2,2-(Dimethyl-$^{14}$C)malonate (XXI) [50]

A 2-l, three-necked flask was fitted with a Claisen adapter containing a mechanical stirrer and a gas inlet tube, a Friedrichs condenser (cooled with circulating alcohol at 10°) with a drying tube and a Liebig condenser (water cooled) with a drying tube and a suspended thermometer which reached into the flask. The glassware was previously dried in an oven, assembled while hot and allowed to cool under a nitrogen atmosphere.

The Friedrichs condenser was detached and 500 ml. of ethanol (previously treated with sodium)[51] was distilled into the flask. Sodium (12.7 g., 0.559 mole), in small pieces was added under a nitrogen atmosphere at such a rate as to maintain the temperature below 40°. The Friedrichs condenser was refitted. The gas adapter was replaced by a pressure-equalizing addition funnel containing ethyl 2-methylmalonate (XIX) (87.1 g., 0.500 mole), which was added over a period of one hour at such a rate as to maintain the temperature below 20°. The flask was then cooled in an ice bath and 1.0 mc. of methyl iodide-$^{14}$C (XX-$^{14}$C) (International Chemical and Nuclear Corp., Irvine, Ca.), diluted to 83.5 g. (0.587 mole) with freshly distilled methyl iodide (XX) was added dropwise over a period of 15 min. The reaction mixture was gently refluxed for 12 hr.

A 5-ml. aliquot was removed and evaporated under vacuum

to give a yellow liquid and some white solid. The addition of water caused the solid to dissolve. The organic layer was separated and the aqueous layer was extracted with several portions of ether. The organic layers were combined, dried over magnesium sulfate and filtered. The solvent was evaporated under vacuum to yield a clear, pale yellow liquid. Glc (Col. 1. 80°) indicated that a few percent of ethyl 2-methylmalonate (XIX) remained.

Sodium (1.0 g.) was added to the reaction mixture with stirring. The flask was cooled in an ice bath and methyl iodide (XX) (20 g., 0.14 mole) was added dropwise. The reaction mixture was stirred for 15 min. and then gently refluxed for 5 hr. Another 5-ml. aliquot was removed and worked up as the first aliquot. Glc (Col. 1, 80°) indicated that the reaction was complete.

The entire reaction mixture was treated as were the aliquots, above, to yield 72.2 g. of ethyl 2,2-(dimethyl-$^{14}$C)malonate (XXI) (76.7% based on ethyl 2-methylmalonate (XIX) which was reduced to 2,2-(dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) without further purification.

B) Reduction of Ethyl 2,2-(Dimethyl-$^{14}$C)malonate(XXI)[52]

A 1-l. three-necked flask was fitted with a Claisen adapter containing a mechanical stirrer and a gas inlet tube, a Friedrichs condenser (cooled with circulating alcohol at 10°) with a drying tube and a 150-ml. pressure-equalizing addition funnel. All of the glassware was previously dried in an oven, assembled while hot and allowed to cool

under a nitrogen atmosphere.

Lithium aluminum hydride (47.9 g., 1.26 moles) was added, with stirring, to 100 ml. of anhydrous ether in the flask. To the resulting grey slurry, 72.2 g. (3.84 moles) of ethyl 2,2-(dimethyl-$^{14}$C)malonate (XXI), (p. 101) was added over a period of 2.5 hr. The reaction mixture was then gently refluxed for 3.5 hr., stirred at room temp. for an additional 4.5 hr. and cooled in an ice bath.

Water (300 ml.) was added dropwise with stirring to yield a thick white paste. The paste dissolved by adding, with vigorous stirring, 50 ml. of 10% HCl followed by 400 ml. of conc. HCl. The organic layer was separated. The aqueous layer was extracted with twelve 200-ml. portions of ether. The organic layers were combined, dried over magnesium sulfate and filtered. The solvent was evaporated under vacuum to give 19.5 g. of an oily white solid. The solid was slurried in a few ml. of cold 60:40 benzene/hexane and filtered to give 15.9 g. of a white crystalline solid.

The aqueous layer was transferred to a continuous extractor and extracted with ether for several days. The etheral solution was separated, dried over magnesium sulfate and filtered. The ether was evaporated under vacuum to yield 17.1 g. of a white solid. The two white solids, above, were combined and recrystallized to give 2,2-(dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) (68.8%), m.p. 127-128° (lit.[53] m.p. 127°). Diol I-$^{14}$C was further recrystallized from 60:40

benzene/hexane (20 ml./g.) to constant molar act. (2.187 mc./mole). Nmr ($CDCl_3$) δ0.87 (s, 6H, $CH_3$) 3.43 (broad s, 4H, $CH_2$) 4.21 (broad s, 2H, OH).

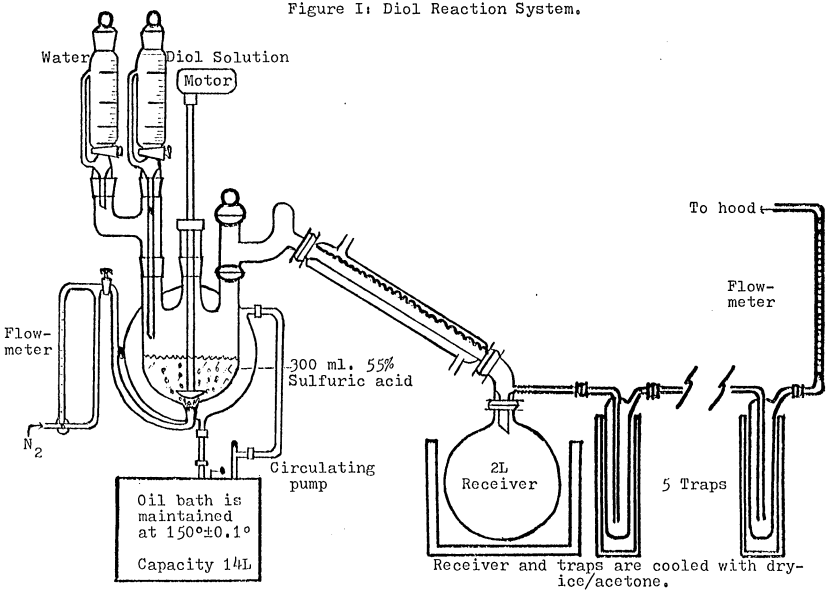
II Reaction of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) with Sulfuric Acid

A) Dehydration-Rearrangement of 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C)

A diagram of the apparatus specifically designed for this reaction is shown in fig. I, p. 105. A 2-l. jacketed three-necked flask with a fritted glass disc at the bottom served as the reaction vessel. The vessel was fitted with a mechanical stirrer, a Claisen adapter containing two pressure-equalizing addition funnels and a Claisen distillation head. A Kronbitter condenser and a vacuum adapter connected the distilling head to a 2-l. receiving flask. The receiving flask was in turn connected to a series of five traps and a flowmeter. The distillation head (and the neck of the reaction vessel to which it was attached), Kronbitter condenser, receiving flask and the traps all contained spherical joints for maximum flexibility. Another flowmeter (with a by-pass) was connected through the double wall of the reaction vessel to the fritted disc. Silicone oil was circulated through the flask jacket and maintained at constant temperature by a thermostatted circulating bath (Haake Instrument Corp., Saddle Brook, N.J., model NBS.)

A slight stream of nitrogen was applied through the fritted glass disc. A mixture of 172 ml. of sulfuric acid (96.5-98%) and 132 ml. of water (70.2% acid by wt.) was

Figure I: Diol Reaction System.



added to the reaction vessel. The silicone oil was heated to 155° in the circulator. 2,2-(Dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C) (10.0 g., 0.0960 mole), molar act. 2.187 mc./mole, dissolved in 180 ml. of water, was placed in one addition funnel, and 180 ml. of water was placed in the other. The 2-l. receiving flask and the traps were submerged in dry ice-acetone baths. Water was circulated through the Kronbitter condenser and the external pump of the circulator was opened to circulate silicone oil through the flask jacket. After the temperature was adjusted to a constant 150°±0.1°, the nitrogen flow was increased to 2.6 l./min. The diol solution and water were each added at an approximate rate of 0.5 ml./min. for 6 hr. (0.016 mole diol/hr.). Small adjustments were made in the rate of water addition during the reaction, so that the rate of total addition (water plus aqueous solution) was equal to the rate of distillation. The volume of acid, and thus its concentration, remained constant throughout the reaction. The rate of diol addition was uniform. A constant reading on the flowmeter after the traps insured no pressure build-up in the reaction system.

When the addition of I-$^{14}$C and water was complete, 30 ml. of water was added through the diol addition funnel over a period of 25 min.[a] The nitrogen flow was then lowered to a rate just large enough to prevent the acid solution from backing-up through the fritted disc.

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[a]It has been suggested,[9] that the extra reaction time provided by this additional water helps shift the equilibrium

The receiver and traps were removed, stoppered and allowed to warm to room temp. The combined distillate from the receiver and traps, which consisted of two clear liquid phases, was transferred to a separatory funnel, and the upper organic layer was separated. The aqueous layer was extracted with nine 25-ml. portions of dichloromethane. The first eight of these extracts were added to the organic layer and the entire organic phase was dried over magnesium sulfate and filtered. Glc analysis (Col. 1, 80°) of the ninth extract, which was dried and filtered separately, indicated that the extraction was complete.

The volume of the aqueous layer after extraction was 395 ml. (390 ml. of diol solution and water were delivered to the reaction vessel) and the volume of sulfuric acid recovered from the reaction vessel was 295 ml. (the starting volume was 290 ml.). Thus the acid strength was the same at the beginning and end of the reaction.

The organic phase was concentrated to a volume of 50 ml. by distillation through a 25 cm. Vigreux column. Glc (Col. 1, 80°) indicated the presence of dichloromethane, 2-methylbutanal

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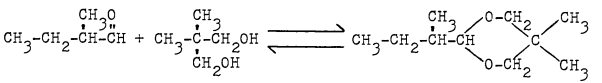
below to the left, resulting in a greater yield of carbonyl products.



II I IV

(II)[a1] (9.0% yield) and 3-methyl-2-butanone (III)[b1] (55.4% yield) in the residue.

B) Isolation of 3-Methyl-2-butanone (III)[b1]

In a 100-ml. flask, equipped with a magnetic stirring bar, 52.1 g. (0.307 mole) of silver nitrate was dissolved in 50 ml. of water. A cooled solution of 25.0 g. (0.626 mole) of NaOH in 50 ml. of water was added, which resulted in the formation of a thick grey-black precipitate. The concentrated organic phase (p. 107) was added to the flask with 80 ml. of water.[54] Two condensers, in series, were connected to the flask, and the mixture was heated at 90° for 16 hours.

The cooled reaction mixture was filtered with suction through a fritted glass funnel with a dry ice-acetone trap in the line. The filtrate and liquid recovered from the trap consisted of two clear liquid phases. The organic layer was separated, and the aqueous layer was extracted with five 15-ml. portions of dichloromethane. The first four extracts were combined with the organic layer and the entire organic phase was dried over magnesium sulfate and filtered. Glc (Col. 1, 78°) of the fifth extract, which was dried and filtered separately, indicated that the extraction was complete. Glc (Col. 1, 78°) of the organic phase indicated that 3.63 g. (43.9% yield) of ketone III [b1] was present. The organic phase was distilled through a 25 cm. Vigreux column to yield 1.55 g. (18.7%) of ketone III[ b1 ], b.p. 91-93° (lit.[55] b.p. 94.2°), which glc (Col.

1 & 2, 75°) indicated was > 96% pure. The product was diluted to 4.0 g. with unlabeled ketone III and was redistilled. Glc (Col. 1 and 2, 75°) indicated that the 3.25 g. of 3-methyl-2-butanone (III)[b1] (b.p. 93-94°) obtained was > 98% pure. Nmr ($CDCl_3$) δ1.11 (d, 6H, $C(CH_3)_2$) 2.16 (s, 3H, $CH_3$) 2.63 (m, 1H, CH). The molar act. was 843.8 μc./mole (see Table VII, p. 38).

The dehydration of diol I-$^{14}C$ and isolation of ketone III[b1] was run in duplicate. In the second run, the yields from the dehydration-rearrangement of I-$^{14}C$, as detected in the dichloromethane residue were 9.1% yield II and 55.4% yield III. After oxidation of II[b1], 3.41 g. (41.1%) ketone III[b1] was detected in the organic phase. Upon isolation and dilution the 4.27 g. of ketone III[b1] (b.p. 90-94°) obtained was found to be > 99% pure. The molar act. was 241.9 μc./mole.

III Carbon-14 Analysis of 3-Methyl-2-butanone (III)[bl]

Ketone III[bl], isolated from the two dehydration-rearrangement reactions of diol I-$^{14}$C (p. 104), was degraded, and carbon-14 analyses were performed on the fragments. The molar activities of all the derivatives of III[bl], from both run 1 and run 2, are listed in Table VII, p. 38.

A) Semicarbazone Derivative of 3-Methyl-2-butanone (III)[bl].[56]

Semicarbazide hydrochloride (XVII) (262 mg., 2.35 mmoles.) and sodium acetate (412 mg., 3.03 mmoles.) were placed in a 25-ml. flask and dissolved in 1 ml. of water. 3-Methyl-2-butanone (III)[bl] (203 mg., 2.36 mmoles.) was pipetted into the flask with 0.4 ml. of 95% aqueous ethanol. The flask was stoppered and shaken vigorously. A white solid precipitated which was dissolved by warming on a steambath. Upon standing for 14 hr., the white solid crystallized. The mixture was refrigerated at least 24 hr., filtered with suction and the solid was washed with three 5-ml. portions of water. After drying under vacuum the semicarbazone (XXIII)[bl]{1-4,4} (69.4%) obtained was recrystallized to constant m.p., 113-114° (lit.[57] m.p. 114°) and molar act., 833.7 μc./mole, with 13% aqueous ethanol (8.7 ml./g.). The molar act. of XXIII[bl]{1-4,4} used for run 2 was 240.8 μc./mole (Table VII, p. 38).

B) Bromoform Reaction of 3-Methyl-2-butanone (III)[bl][58]

A 100-ml. three-necked flask was equipped with a thermometer and a magnetic stirrer. A solution of 5.72 g. (143

mmoles.) of NaOH in 35 ml. of water was added and cooled in an ice-water bath. The solution was stirred and 3.08 g. (19.2 mmoles.) of bromine was added dropwise at such a rate as to maintain the temp. below 5°. 3-Methyl-2-butanone (III) [bl] (317 mg., 3.68 mmoles.) was pipetted into the flask with 15 ml. of water. The reaction mixture was stirred for 2 hr. below 5°, warmed to room temp. and stirred for another 18 hr. The carbon tetrabromide ($CBr_4$) which formed was distilled with 10 ml. of water, filtered with suction and washed with three 5-ml. portions of 50° water. This crude $CBr_4$ was dissolved in ether, dried over magnesium sulfate and filtered, and the solvent was evaporated under vacuum from an ice-water bath. The $CBr_4$ was further purified by sublimation at 4 mm. from a warm water (40°) bath to yield $CBr_4$ (XXIV)[bl]{1} (53.2%) which was sublimed to constant m.p., 94°, (lit. [59] m.p. 94.3°) and molar act. 378.8 μc./mole. The molar act. of XXIV[bl]{1} from run 2 was 103.1 μc./mole (Table VII, p. 38).

The remaining 40 ml. of basic reaction mixture, containing sodium isobutyrate (XXV)[bl]{2-4,4}, was acidified with conc. phosphoric acid to pH 2. The bromine color that formed upon acidification was dispelled with a small portion of sodium bisulfite. The clear, acidified solution was distilled to dryness, and the distillate was titrated to pH 8.2 (phenolphthalein) with 1.0 N NaOH. The neutralized distillate was concentrated to 5 ml. To 4.5 ml. of the concentrate containing 1.76 mmoles of XXV[bl]{2-4,4}, 442 mg. (1.59 mmoles.) of p-bromophenacyl bromide (XXVI) in 10.5 ml. of

86% aqueous ethanol was added. The amount of sodium isobutyrate (XXV) present was based upon the titration with NaOH and from the yield of $CBr_4$ (XXIV)[bl]{1}. The solution, which formed on heating, was refluxed for 40 min. The p-bromophenacyl isobutyrate (XXVII)[bl]{2-4,4}, which formed on cooling, was filtered with suction and washed with two 5-ml. portions of water and one 5-ml. portions of cold 63.4% aqueous ethanol. After drying under vacuum, the p-bromophenacyl isobutyrate (XXVII)[bl]{2-4,4} (57.9%) was recrystallized to constant m.p., 76-77°, (lit.[60] m.p. 77°) and molar act., 467.8 μc./mole, with 63.4% aqueous ethanol (33 ml./g.). The molar act. of XXVII[bl]{2-4,4} from run 2 was 135.2 μc./mole (Table VII, p. 38).

C) Baeyer-Villiger Degradation Route

1) Oxidation of 3-Methyl-2-butanone (III)[bl].[61]

A 50-ml. flask was equipped with a magnetic stirring bar and two condensers (in series) with a drying tube. To 1.20 g. (13.9 mmoles.) of 3-methyl-2-butanone (III)[bl] in 14 ml. of dichloromethane, 3.81 g. of 79.9% m-chloroperbenzoic acid (XXVIII) (17.6 mmoles.) was added, and the resulting solution was refluxed in the dark for 19 hr. A white precipitate of m-chlorobenzoic acid formed. Glc (Col. 1, 75°) of the dichloromethane solution indicated the absence of the starting ketone III[bl]. Sodium carbonate (1 M, 12 ml.) was added to dissolve precipitated acid, and 0.4 g. of sodium bisulfite was added in several portions with stirring to destroy excess peracid. Stirring was continued until two

clear layers were obtained. NaOH (10%, 2 ml.) was added to adjust the pH to 10. The organic layer was separated and the aqueous layer was extracted with three 2.5-ml. portions of dichloromethane. The organic layers were combined, dried over magnesium sulfate and filtered into a 100-ml. flask. Glc (Col. 2, 50°) indicated that 0.94 g. (66%) of isopropyl acetate (XXIX)[bl]{1-4,4} was present in 20 ml. of dichloromethane solution.

2) Hydrolysis of Isopropyl Acetate (XXIX)[bl]{1-4,4}

A solution of 4.24 g. (0.106 mole) of NaOH in 30 ml. of water was added to the 100-ml. flask (see above) containing the dichloromethane solution of isopropyl acetate (XXIX)[bl]{1-4,4}. A magnetic stirring bar was added and two condensers (in series) were attached. The mixture was refluxed with stirring for 40 hr. Glc (Col. 2, 40°) of the dichloromethane layer indicated the absence of XXIX[bl]{1-4,4}. The organic layer was separated, and the aqueous layer was extracted with seventeen 5-ml. portions of dichloromethane. The extracts were combined with the organic layer and the entire organic phase was dried over magnesium sulfate and filtered. Glc (Col. 1, 40°) indicated the presence of 0.358 g. (64.8%, based on XXIX[bl]{1-4,4}) isopropanol (XXXI)[bl]{3,4,4}.

The basic aqueous layer from the hydrolysis was acidified with conc. phosphoric acid and distilled to dryness. The distillate was titrated with 1.0 N NaOH to pH 8.2 (phenolphthalein) and the resulting solution concentrated

to 11 ml. The sodium acetate (XXX)[bl]{1,2} (6.41 mmoles.) present in this concentrate was derivatized with 5.75 mmoles. of p-bromophenacyl bromide (XXVI) in 36 ml. of 47.5% aqueous ethanol following the procedure for the preparation of p-bromophenacyl isobutyrate (XXVII)[bl]{2-4,4}, p. 111. The p-bromophenacyl acetate (XXXII)[bl]{1,2} (78.4%) obtained was recrystallized to constant m.p., 84-85° (lit.[60] m.p. 85°) and molar act., 401.8 μc./mole, with 47.5% aqueous ethanol (35 ml./g.). The molar act. of XXXII [bl]{1,2} from run 2 was 115.4 μc./mole (Table VII, p. 38).

A portion of the dichloromethane solution containing isopropanol (XXXI)[bl]{3,4,4}, was used for the preparation of a 3,5-dinitrobenzoate derivative. 3,5-Dinitrobenzoyl chloride (XXXIII)(353 mg., 1.50 mmoles.) and dry pyridine (0.8 ml.) were dissolved in 21 ml. of dichloromethane containing 1.53 mmoles. of XXXI[bl]{3,4,4} in a 50-ml. flask equipped with a magnetic stirring bar and a condenser with a drying tube. The solution was stirred at reflux for 3 hr. and extracted with four 5-ml. portions of 10% HCl, three 5-ml. portions of 5% sodium bicarbonate and two 5-ml. portions of water. The reaction mixture was then dried over magnesium sulfate, filtered and the solvent was evaporated under vacuum. The crude solid was recrystallized from 7.5 ml. of 95% aqueous ethanol to yield 0.136 g. (35.7%) of isopropyl 3,5-dinitrobenzoate (XXXIV)[bl]{3,4,4}, which was further recrystallized to constant m.p., 122-123°, (lit.[62] m.p. 122.1°) and molar act. 441.5 μc./mole, with 95% aqueous

ethanol (38 ml./g.). The molar act. of XXXIV[bl]{3,4,4} from run 2 was 127.2 μc./mole (Table VII, p. 38).

3) Bromoform Reaction of Isopropanol (XXXI)[bl]{3,4,4}.[63]

The remainder of the dichloromethane solution containing isopropanol (XXXI)[bl]{3,4,4} (p. 113) was extracted with twenty 5-ml. portions of water. The aqueous solution was refrigerated. Bromine (4.50 g., 28.2 mmoles.) was added dropwise to a stirred solution of NaOH (6.67 g., 167 mmoles.) in 50 ml. of water, maintained below 5° with an ice bath, in a 250-ml. three-necked flask equipped with a thermometer and a magnetic stirring bar. The aqueous solution of isopropanol (XXXI)[bl]{3,4,4} was added in 20-ml. portions. The reaction mixture was stirred for three hr. below 5° and for an additional 18 hr. at room temp. The white solid ($CBr_4$) that precipitated was isolated and purified (using the same procedure as for $CBr_4$ (XXIV)[bl]{1}, p. 111) to yield 4.66 g. (25.3% $CBr_4$ (XXIV)[bl]{4}, which was sublimed to constant m.p. 93° (lit.[59] m.p. 94.3°) and molar act., 217.0 μc./mole. The molar act. of XXIV[bl]{4} from run 2 was 62.3 μc./mole (Table VII, p. 38).

Water (100 ml.) was distilled from the basic reaction mixture which contained the second reaction product, sodium acetate (XXX)[bl]{3,4}. The remaining 40 ml. was derivatized with p-bromophenacyl bromide (XXVI), using the same procedure as for the basic reaction mixture containing sodium acetate (XXX)[bl]{1,2}, p. 113. The derivatizing reaction mixture consisted of 1.45 mmoles. of XXX[bl]{3,4} and 0.0403 g.

(1.45 mmoles.) of p-bromophenacyl bromide (XXVI) in 13 ml. of 47.5% aqueous ethanol. The 0.256 g. (68.6%) of p-bromophenacyl acetate (XXXII)[bl][3,4] obtained was recrystallized to constant m.p., 84° (lit.[60] m.p. 85°) and molar act., 223.0 μc./mole, with 47.5% aqueous ethanol (35 ml./g.). The molar act. of XXXII[bl][3,4] from run 2 was 65.0 μc./mole (Table VII, p. 38).

IV Preparation of 3-Methyl-2-butanone-4-$^{14}C$ (III)[b2]

A) Synthesis of Methyl 2-Methylacetoacetate (XXXV)[64]

The apparatus was the same as that described for the synthesis of ethyl 2,2-(dimethyl-$^{14}C$)malonate (XXI), p. 100. The Friedrichs condenser was detached, and 250 ml. of xylene and sodium (3.62 g., 1.57 moles) were added under a nitrogen atmosphere. The Friedrichs condenser was refitted, and the mixture was refluxed. When the sodium melted, vigourous stirring was applied. The heating source was removed and moderate stirring was maintained. On cooling, small sodium spheres were obtained.

The xylene was decanted under a nitrogen atmosphere, and the sodium spheres were washed with two 200-ml. portions of anhydrous ether and two 150-ml. portions of dry benzene. Dry benzene (750 ml.) was then added to cover the sodium spheres. Methyl acetoacetate (XXXV) (174.2 g., 1.50 moles) was added dropwise over a period of 20 min., and the mixture was stirred for 4.5 hr. Methyl iodide (XX) (247.5 g., 1.74 moles) was added dropwise over a period of 15 min. The nitrogen atmosphere was removed. The reaction mixture was stirred for 18 hr. at room temp. and then gently refluxed for 24 hr.

When the stirring was stopped, a white solid settled out of a pale yellow liquid. A 10-ml. aliquot was evaporated under vacuum and filtered. Nmr analysis indicated that 10% methyl acetoacetate (XXXV) remained. Sodium (3.6 g.,

0.16 mole) and methyl iodide (XX) (24.5 g., 0.17 mole) were added and the reaction mixture was stirred for 24 hr. at room temp. and for an additional 24 hr. at reflux. The mixture was filtered, and the filtrate was evaporated under vacuum to yield 153.2 g. of a yellow liquid. This liquid was distilled through a 25 cm. Vigreux column, b.p. 80-84°/19 mm. (lit.[65] b.p. 80°/20 mm.) to yield a clear, colorless liquid. Glc (Col. 1, 116°) indicated that the liquid consisted of 89.8% methyl 2-methylacetoacetate (XXXV), 8.7% methyl 2,2-dimethylacetoacetate (XXXVI) and 1.5% methyl acetoacetate (LXXV). This mixture was used to synthesize methyl 2,2-(dimethyl-$^{14}$C)acetoacetate (XXXVI) without further purification.

B) Synthesis of Methyl 2,2-(Dimethyl-$^{14}$C)acetoacetate (XXXV)

The apparatus was the same as that described for the synthesis of ethyl 2,2-(dimethyl-$^{14}$C)malonate (XXI) p. 100, except that a 500-ml. three-necked flask was employed. Small solid spheres of sodium (1.69 g., 73.5 mmoles.) in 100 ml. of benzene were prepared as in the synthesis of methyl 2-methylacetoacetate (XXXV), p. 117. After the flask had been cooled in an ice-water bath for 10 min., methyl 2-methylacetoacetate (XXXV) (10.0 g., 69.0 mmoles.) above, was added dropwise over a period of 10 min. The mixture was stirred at room temp. for 11 hr. Methyl iodide-$^{14}$C (YX-$^{14}$C) (1.0 mc., International Nuclear Corp., Irvine, Ca.), diluted with 25 ml. of benzene was added, followed by unlabeled methyl iodide (XX)

(10.8 g., 76.0 mmoles.). The nitrogen atmosphere was removed. The reaction mixture was allowed to stand, without stirring, at room temp. for 9 hr. and was refluxed with moderate stirring for 18 hr.

When the stirring was stopped, a white solid settled out of a yellow liquid. The mixture was filtered with suction. The clear, yellow filtrate was distilled until two thirds of its volume remained. Glc (Col. 1, 120°) indicated the concentrated filtrate to contain 5% methyl 2-methylacetoacetate (XXXV). The concentrated filtrate was added to 0.12 g. (30.0 mmoles.) of sodium (in small pieces) in 25 ml. of benzene in the original flask. The reaction mixture was stirred for 4 hr. during which time some white solid formed. Methyl iodide (XX) (0.68 g., 48 mmoles.) was washed in with 5 ml. of benzene. The reaction mixture was refluxed with stirring for 15 hr. Glc (Col. 1, 115°) indicated the absence of methyl 2-methylacetoacetate (XXXV).

The reaction mixture was evaporated under vacuum to 25 ml. of a deep orange-red oil and a yellow solid. Water (20 ml.) was added to dissolve the solid. The organic layer was separated, and the aqueous layer was extracted several times with ether. The organic layer and extracts were combined, dried over magnesium sulfate and filtered. The solvent was removed under vacuum to yield a clear, yellow liquid. The 1.80 g. (17.5%) methyl 2,2-(dimethyl-$^{14}$C)acetoacetate (XXXVI) obtained was decarboxylated to 3-methyl-2-butanone-4-$^{14}$C (III)[b2], without further purification.

C) Decarboxylation of Methyl 2,2-(Dimethyl-$^{14}$C)acetoacetate (XXXVI)[66]

Methyl 2,2-(dimethyl-$^{14}$C)acetoacetate (XXXVI) (1.27 g., 8.80 mmoles.) was diluted to 2.58 g. (17.9 mmoles.) with unlabeled ester XXXVI in a 10-ml. flask equipped with a magnetic stirrer. Calcium iodide tetrahydrate (3.74 g., 10.2 mmoles.) (Ventron Co., Danvers, Mass.) was added. The flask was fitted with a 10 cm. Vigreux column and a distillation head and immersed in an oil bath. When the bath temp. reached 137° a reaction occurred, and a two-phase distillate was collected. After cooling, 1.05 g. (12.2 mmoles.) of unlabeled 3-methyl-2-butanone (III) was added to the flask, and the distillation was continued in order to remove any 3-methyl-2-butanone-4-$^{14}$C (III)[b2] held up in the column. The two-phase distillate was placed in a 25-ml. separatory funnel with several ml. of dichloromethane. The aqueous layer was removed and the organic phase was washed with seven 3-ml. portions of water. The organic layer was dried over magnesium sulfate and filtered. Glc (Col. 1, 80°) indicated the presence of methyl iodide (XX), dichloromethane, a very small amount of methanol and 3-methyl-2-butanone-4-$^{14}$C (III)[b2].

Freshly distilled unlabeled 3-methyl-2-butanone (III) (3.0 g., 35 mmoles.) was added to the mixture containing 3-methyl-2-butanone-4-$^{14}$C (III)[b2] in a 10-ml. flask. The flask was fitted with a 25 cm. Vigreux column and the organic phase was distilled to yield 2.04 g. of 3-methyl-

2-butanone-4-$^{14}$C (III)[b2], b.p. 92-94° (lit.[55] b.p. 94.2°). Glc (Col. 1, 80°) indicated that the ketone III[b2] was approx. 99% pure. The 3-methyl-2-butanone-4-$^{14}$C (III)[b2] was diluted to 6.88 g. Of the activity in the methyl iodide-$^{14}$C (XX-$^{14}$C) (1.0 mc.) used in the synthesis of methyl 2,2-(dimethyl-$^{14}$C)acetoacetate (XXXV), 3.5% remained in 3-methyl-2-butanone-4-$^{14}$C (III)[b2].

A portion of ketone III[b2] (4.20 ml., 4.88 mmoles.) was set aside for reaction with 55% $H_2SO_4$ (p. 125). The remainder of III[b2] was transferred to a vial, with a minimal amount of washing with unlabeled ketone III, for degradation (p. 122). The molar activity of this slightly diluted ketone III[b2] was determined to be 432.0 μc./mole.

V Carbon-14 Analysis of 3-Methyl-2-butanone-4-$^{14}$C (III)[b2]

The procedure for the carbon-14 analysis of 3-methyl-2-butanone (III)[b1], p. 110, was followed. The molar activities are listed in Table V, p. 32.

A) Semicarbazone Derivative of 3-methyl-2-butanone-4-$^{14}$C (III)[b2]

The reaction mixture consisted of 244 mg. (2.83 mmoles.) of ketone III[b2], 308 mg. (2.76 mmoles.) of semicarbazone hydrochloride (XXII) and 487 mg. (3.58 mmoles.) of sodium acetate in 9.8 ml. of 26% aqueous ethanol. The semicarbazone XXIII[b2]{1-4,4} (33%) obtained was recrystallized to constant m.p., 113-114° (lit.[57] m.p. 114°) and molar act., 433.9 μc./mole.

B) Bromoform Reaction of 3-Methyl-2-butanone-4-$^{14}$C (III)[b2]

The reaction mixture consisted of 278 mg. (3.23 mmoles.) ketone III[b2], 2.11 g. (52.8 mmoles.) of NaOH and 3.05 g. (19.1 mmoles.) of bromine in 50 ml. of water. The $CBr_4$ (XXIV)[b2]{1} (17.5%) obtained was sublimed to constant m.p., 93° (lit.[59] m.p. 94.3°) and molar act., 18.6 μc./mole.

Sodium isobutyrate (XXV)[b2]{2-4,4} (3.40 mmoles.), in the basic reaction mixture, was derivatized with 0.806 g. (2.90 mmoles.) of p-bromophenacyl bromide (XXVI) in 19 ml. of 57% aqueous ethanol. The p-bromophenacyl isobutyrate (XXVII)[b2]{2-4,4} (64.3%) obtained was recrystallized to constant m.p., 77° (lit.[60] m.p. 77°) and molar act., 440.6 μc./mole.

C) Baeyer-Villiger Degradation Route

1) Oxidation of 3-Methyl-2-butanone-4-$^{14}$C (III)[b2]

The reaction mixture consisted of 1.22 g. (14.2 mmoles.) of ketone III[b2] and 3.85 g. (17.8 mmoles.) of 79.9% m-chloroperbenzoic acid (XXVIII) in 14 ml. of dichloromethane. Glc (Col. 1, 60°) indicated that 12.0 mmoles. (85%) of isopropyl acetate (XXIX)[b2]{1-4,4} was present in the dichloromethane solution.

2) Hydrolysis of Isopropyl Acetate (XXXIX)[b2]{1-4,4}

The reaction mixture consisted of 12.0 mmoles. of ester XXIX[b2]{1-4,4} in 20 ml. of dichloromethane and 2.93 g. (73.2 mmoles.) of NaOH in 30 ml. of water. After dichloromethane extraction, the remaining basic aqueous phase contained 10.5 mmoles. of sodium acetate (XXX)[b2]{1,2}, which was derivatized with 2.57 g. (9.26 mmoles.) of p-bromophenacyl bromide (XXVI) in 36 ml. of 47.5% aqueous ethanol. The 2.22 g. (93.3%) of p-bromophenacyl acetate (XXXII)[b2]{1,2} obtained was recrystallized to constant m.p., 84-85° (lit.[60] m.p. 85°) and molar act., 0.65 μc./mole.

Isopropanol (XXXI)[b2]{3,4,4} (2.5 mmoles.) in a portion (23 ml.) of the dichloromethane extract of the hydrolysis reaction of isopropyl acetate (XXIX)[b2]{1-4,4} was derivatized with 539 mg. (2.43 mmoles.) of 3,5-dinitrobenzoyl chloride (XXXIII) in the presence of 1.5 ml. of dry pyridine. The 0.211 g. (36%) of isopropyl 3,5-dinitrobenzoate (XXXIV)[b2]{3,4,4} obtained was recrystallized to constant m.p., 122° (lit.[62] m.p. 122.1°) and molar act., 437.9 μc./mole.

3) Bromoform Reaction of Isopropanol (XXXI)[b2]{3,4,4}

Isopropanol (XXXI)[b2]{3,4,4} (7.4 mmoles.) in the remainder of the dichloromethane extract of the hydrolysis reaction of isopropyl acetate (XXIX)[b2]{1-4,4} was extracted with water and reacted with 11.0 g. (274 mmoles.) of NaOH and 7.29 g. (45.6 mmoles.) of bromine (total vol. of water 150 ml.). The 0.712 g. (29.3%) of $CBr_4$ (XXIV) [b2]{4} obtained was sublimed to constant m.p., 93-94° (lit.[59] m.p. 94.3°) and molar act., 219.2 μc./mole.

The 6.15 mmoles. of sodium acetate (XXX)[b2]{3,4} in the basic reaction mixture was derivatized with 1.46 g. (5.24 mmoles.) of p-bromophenacyl bromide (XXVI) in 25 ml. of 47.5% aqueous ethanol. The 0.605 g. of p-bromophenacyl acetate (XXXII)[b2]{3,4} obtained was recrystallized to constant m.p., 84-85° (lit.[60] m.p. 85°) and molar act., 217.8 μc./mole.

VI Attempted Detection of Isomerized and Carbon-14 Scrambled Products of 3-Methyl-2-butanone-4-$^{14}$C (III)[b2]

A) Reaction of 3-Methyl-2-butanone-4-$^{14}$C (III)[b2] with 55% Sulfuric Acid

The procedure and apparatus was the same as that for the dehydration-rearrangement of 2,2-(dimethyl-$^{14}$C)-1,3-propanediol (I-$^{14}$C), p. 104. 3-Methyl-2-butanone-4-$^{14}$C (III) [b2] (4.20 ml., 4.88 mmoles.) (p. 121) was placed in a 6-ml. pressure-equalizing addition funnel and 150 ml. of water was placed in the other addition funnel. The ketone III[b2] was added in 0.3-ml. portions at 10 min. intervals and water was added dropwise to maintain constant acid volume in the reaction vessel. The temp. during the reaction was maintained at 150° ± 0.2°. After addition of the ketone III was complete, 15 ml. of water was added over a period of 20 min. Glc (Col. 1, 75°) indicated that the conc. dichloromethane solution contained 44 mmoles. (91% recovery) of 3-methyl-2-butanone (III)[b3].

B) Isolation of 3-Methyl-2-butanone (III)[b3].

The organic phase was heated with silver oxide reagent, consisting of NaOH (18.4 g., 0.460 mole) and silver nitrate (38.6 g., 0.225 mole) in 100 ml. of water, for 18 hr. at 80° as described on p. 108. Glc (Col. 1, 75°) indicated that the organic phase contained only 3-methyl-2-butanone (III) [b3] and dichloromethane. After distillation, 1.41 g. (33.6%) of 3-methyl-2-butanone (III)[b3], b.p. 93-94° (lit.[55]

b.p. 94.2°) was collected. Glc (Col. 2, 75°) indicated that ketone III[b3] was greater than 99% pure. The molar act. of ketone III[b3] was 476.3 μc./mole.

VII Carbon-14 Analysis of 3-Methyl-2-butanone (III)[b3]

The procedure for the carbon-14 analysis of 3-methyl-2-butanone (III)[b1], p. 110, were followed. The molar activities are listed in Table V, p. 32.

A) Semicarbazone Derivative of 3-methyl-2-butanone (III)[b3]

The reaction mixture consisted of 157 mg. (1.82 mmoles.) of ketone III[b3] , 203 mg. (1.82 mmoles.) of semicarbazide hydrochloride (XXII) and 320 mg. (2.35 mmoles.) of sodium acetate in 6.5 ml. of 23% aqueous ethanol. The semicarbazone XXIII[b3]{1-4,4} (51.7%) obtained was recrystallized to constant m.p., 113-114° (lit.[56] m.p. 114°) and molar act., 473.4 μc./mole.

B) Bromoform Reaction of 3-Methyl-2-butanone (III)[b3]

The reaction mixture consisted of 250 mg. (2.90 mmoles.) of ketone III[b3], 3.45 g. (86.3 mmoles.) of NaOH and 1.88 g. (11.8 mmoles.) of bromine in 50 ml. of water. The $CBr_4$ (XXIV)[b3]{1} (17.5%) obtained was sublimed to constant m.p., 93° (lit.[59] m.p. 94.3°) and spec. act., 22.2 μc./mole.

Sodium isobutyrate (XXV)[b3]{2-4,4} (2.41 mmoles.), in the basic reaction mixture, was derivatized with 0.591 g. (2.12 mmoles.) of p-bromophenacyl bromide (XXVI) in 17 ml. of 63% aqueous ethanol. The p-bromophenacyl isobutyrate (XXVII)[b3]{2-4,4} (56.6%) obtained was recrystallized to constant m.p., 77° (lit.[60] m.p. 77°) and molar act., 472.6 μc./mole.

C) Baeyer-Villiger Degradation Route

1) Oxidation of 3-Methyl-2-butanone (III)[b3]

The reaction mixture consisted of 1.00 g. (11.6 mmoles.) of ketone III[b3] and 2.45 g. (14.2 mmoles.) of 79.9% m-chloroperbenzoic acid (XXVIII) in 12 ml. of dichloromethane. Glc (Col. 1, 60°) indicated that 7.73 mmoles. (67%) of isopropyl acetate (XXIX)[b3]{1-4,4} were present in the dichloromethane solution.

2) Hydrolysis of Isopropyl Acetate (XXIX)[b3]{1-4,4}

The reaction mixture consisted of 12.0 mmoles. of ester XXIX[b3]{1-4,4} in 20 ml. of dichloromethane and 2.84 g. (71.0 mmoles.) of NaOH in 30 ml. of water. After dichloromethane extraction, the remaining basic aqueous phase contained 4.65 mmoles. of sodium acetate (XXX)[b3]{1,2} which was derivatized with 1.11 g. (4.00 mmoles.) of p-bromophenacyl bromide (XXVI) in 16 ml. of 47.5% aqueous ethanol. The 0.790 g. (76.8%) of p-bromophenacyl acetate (XXXII)[b3]{1,2} obtained was recrystallized to constant m.p., 84-85° (lit.[60] m.p. 85°) and molar act., 0.35 μc./mole.

Isopropanol (XXXI)[b3]{3,4,4} (2.0 mmoles.) in a portion (19 ml.) of the dichloromethane extract of the hydrolysis reaction of isopropyl acetate (XXIX)[b3]{1-4,4} was derivatized with 445 mg. (1.93 mmoles.) of 3,5-dinitrobenzoyl chloride (XXXIII) in the presence of 1.0 ml. of dry pyridine. The 86.3 mmoles. (17.6%) of isopropyl 3,5-dinitrobenzoate (XXXIV) [b3]{3,4,4} obtained was recrystallized to constant m.p., 123° (lit.[62] m.p. 122.1°) and molar act., 474.1 μc./mole.

3) Bromoform Reaction of Isopropanol (XXXI)[b3]{3,4,4}

Isopropanol (XXXI)[b3]{3,4,4} (7.4 mmoles.) in the remainder of the dichloromethane extract of the hydrolysis reaction of isopropyl acetate (XXIX)[b3]{1-4,4} was extracted with water and reacted with 9.96 g. (249 mmoles.) of NaOH and 6.58 g. (41.2 mmoles.) of bromine (total vol. of water 150 ml.). The 0.641 g. (23.8%) of $CBr_4$ (XXIV)[b3]{4} obtained was sublimed to constant m.p., 93-94° (lit.[59] m.p. 94.3°) and molar act., 241.2 μc./mole.

The 3.63 mmoles. of sodium acetate (XXX)[b3]{3,4} in the basic reaction mixture was derivatized with 0.810 g. (2.91 mmoles.) of p-bromophenacyl bromide (XXVI) in 20 ml. of 46.5% aqueous ethanol. The 0.436 g. (58.3%) p-bromophenacyl acetate (XXXII)[b3]{3,4} obtained was recrystallized to constant m.p., 83-84° (lit.[60] m.p. 85°) and molar act., 237.0 μc./mole.

VIII Reaction of 2,2-Dimethyl-1,3-propanediol-$(OD)_2$ (Ia) with 55% Deuteriosulfuric Acid

A) Preparation of 55% Deuteriosulfuric Acid

Deuteriosulfuric acid ($D_2SO_4$) was prepared according to the method of Roberts.[67] In a hood, a 2-l. flask was equipped with a 1-l. pressure-equalizing addition funnel with a drying tube. After the addition of 270 ml. (14.9 moles) of deuterium oxide ($D_2O$) (99.8%d), the flask was immersed in a dry ice-acetone bath. As a precaution, a plexiglass shield was set up in front of the flask. Stabilized sulfur trioxide (Sulfan, Baker and Adamson Co., Morristown, N.J.) (473 ml., 11.3 moles) was added dropwise (cautiously) over a period of 2 hr. The white solid which formed was allowed to melt slowly over a period of 16 hr., yielding a clear, colorless liquid (final volume, 740 ml.). The acid strength was determined by titration to be 34.1N (91.1%). Nmr analysis determined the $D_2SO_4$ to be 99.7% free of hydrogen. $D_2SO_4$ (55%) was prepared by diluting 181 ml. of 91.1% acid with 119 ml. of $D_2O$.

B) Preparation of 2,2-Dimethyl-1,3-propanediol-$(OD)_2$ (Ia)

2,2-Dimethyl-1,3-propanediol (I) (34.8 g., 0.334 mole) was dissolved in 20 ml. (1.10 moles) of $D_2O$, and after thorough mixing, the deuterated water was evaporated under vacuum. This procedure was repeated four times to yield 31.9 g. (0.300 mole) of 2,2-dimethyl-1,3-propanediol-$(OD)_2$ (Ia), m.p. 128°. No hydroxyl proton was discernible by nmr analysis.

C) Dehydration-Rearrangement of 2,2-Dimethyl-1,3-propanediol-$(OD)_2$ (Ia) with 55% Deuteriosulfuric Acid

The procedure was the same as that followed for the dehydration-rearrangement of 2,2-(dimethyl-$^{14}C$)-1,3-propanediol (I-$^{14}C$), p. 104. The reaction vessel contained 278 ml. of 55% $D_2SO_4$ and was maintained at 150.3° ± 0.3°. $D_2O$ (90 ml.) and a solution of 5.31 g. (50.0 mmoles.) of 2,2-dimethyl-1,3-propanediol-$(OD)_2$ (Ia) in 90 ml. of $D_2O$ were added over a period of 185 min. An additional 30 ml. of $D_2O$ was then added over 30 min. After the organic product was extracted with dichloromethane, dried and filtered, most of the dichloromethane was distilled. Glc analysis (Col. 1, 40°) indicated that 6.1 mmoles. (11.8%) of 2-methylbutanal (II)[al] and 23.2 mmoles. (43.8%) of 3-methyl-2-butanone (III)[al] had been obtained. After the reaction 270 ml. of $D_2SO_4$ was recovered. This reaction was run in duplicate. Glc analysis of the dichloromethane residue of the second run indicated that 3.6 mmoles. (6.8%) of 2-methylbutanal (II)[al] and 25.9 mmoles. (48.8%) of 3-methyl-2-butanone (III)[al] had been obtained.

D) Deuterium Analysis of 2-Methylbutanal (II)[al] and 3-Methyl-2-butanone (III)[al]

The conc. dichloromethane solution, containing 2-Methylbutanal (II)[al] and 3-methyl-2-butanone (III)[al], was chromatographed (Col. 3, 100°). The individual carbonyl products were collected in evacuated glass collection vessels and analyzed by mass spectrometry (see Appendix, p. 132).

## Appendix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## I Introduction

In the previously reported study of the deuteriosulfuric acid catalyzed dehydration-rearrangement of 2,2-dimethyl-1,3-propanediol (I),[9] the carbonyl products were isolated by preparative gas chromatography in the usual manner, i.e. by condensation in an open vessel. We have observed by coupled gas chromatography-mass spectroscopy, however, that substantial isotopic fractionation of deuterated 3-methyl-2-butanone (III) takes place during gas chromatography. Multiple mass scans of a single peak of ketone III eluting from the gas chromatograph demonstrated that the forefront of the eluting sample was richest in the more extensively deuterated species. Since the usual methods of collection are not 100% efficient, and, thus differential losses may occur, a total recovery method had to be used for ketone III before the mass spectral analyses could be attempted.

Two total effluent collection techniques have been reported in the literature. One involves trapping the sample containing carrier gas in a Drechsel tube immersed in liquid nitrogen.[68] The other involves collecting the sample containing carrier gas in an evacuated vessel.[69,70] The latter does not require the collection vessel to be immersed in liquid nitrogen during collection of samples. This facilitates the interchange of vessels for collection of multiple samples from a single gas chromatography injection. Only a general procedure and a sketch of an evacuated

vessel has been reported.[69] Adetailed description of such a collection system and its operation is presented.

II Description of the Collection System

The total effluent collection system used in this work is shown in fig. II, fig. III, p. 135 and fig. IV, p. 136. The main components sre a four-way stopcock, two vacuum vessels, a flowmeter and a support system.

Figure II: Schematic Diagram of Total Effluent Gas Chromatography Collection System

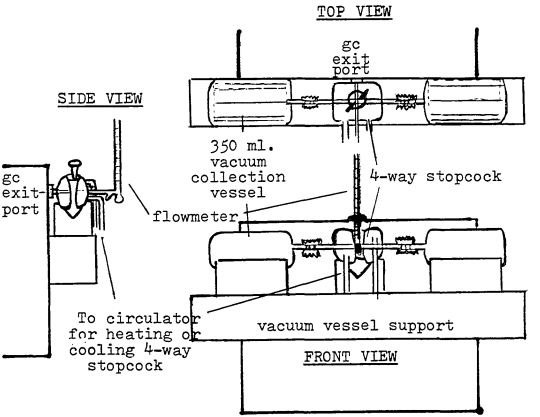


Figure III: Disassembled Collection System

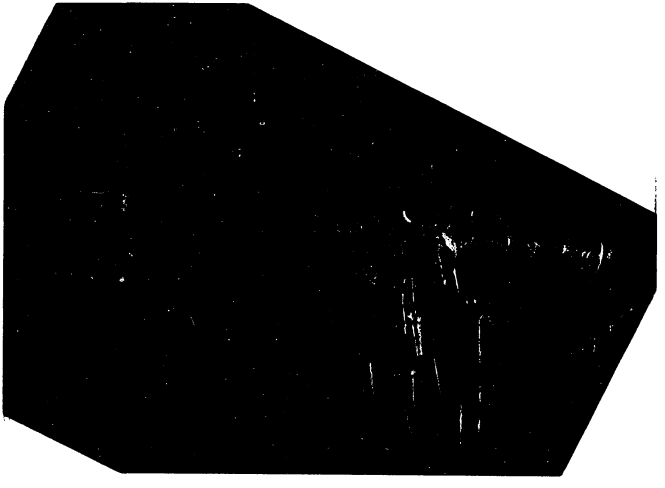


Figure IV: Collection System Attached to the Gas Chromatograph

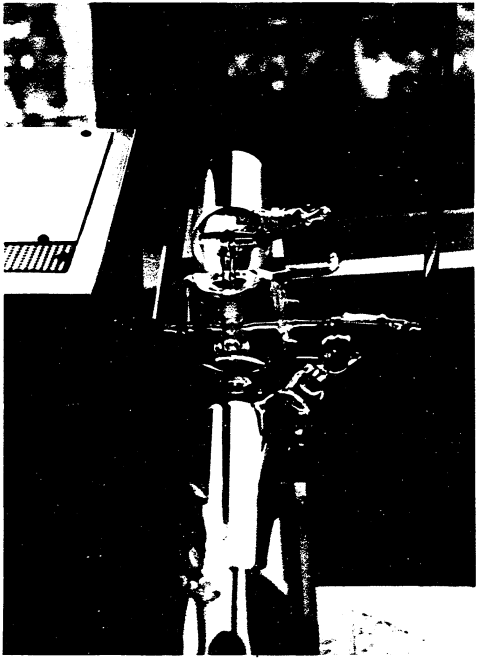


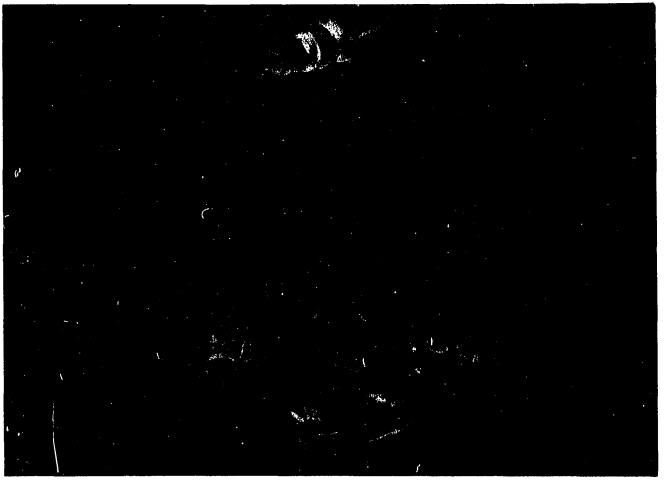
Figure V, p. 138, is a picture of the four-way stopcock. An outer glass housing permits the circulation of water or oil at an elevated temperature. All four extensions of the stopcock are made of capillary tubing (0.250 mm. OD X 0.078 mm. ID). Three of the capillary extensions are fitted with ST 7/25 inner joints. The inner plug consists of a "T"-shaped hole, which allows a connection to be made between the gas chromatograph, the flowmeter and either one of the collection bottles.

Each collection vessel is fitted with a ST 7/25 outer joint through a capillary bore high vacuum stopcock (Eck and Krebs, N.Y., N.Y.) and a ST 24/25 outer joint. The latter is present in order to allow access into the collection vessel for cleaning purposes. The volumes of the vessels were 350 ml. for aldehyde II collection and 450 ml. for ketone III collection. These volumes were chosen to insure complete collection of an aldehyde II peak and a ketone III peak of 5 and 7 min., respectively, with a column flow rate of 60 ml./min.

The flowmeter is fitted with a ST 7/25 outer joint and contains a trap to prevent soap bubbles from backing-up into the collection vessels (see fig. III, p. 135). During collection the flowmeter insures that no ketone escapes and that no disturbance of the separation parameters of the gas chromatograph is created (see p. 139).

The support system is composed of a hollow metal brace screwed to the side of the gas chromatograph (Varian

Figure V: Four-way Stopcock



Aerograph A-90P, thermal conductivity detector) and three wooden wedges which support the four-way stopcock and two collection vessels (fig. IV, p. 136).

III Assembly and Collection of Samples

For assembly, the four-way stopcock is slid into place at the exit port. The blunt end capillary extension is attached to the gas chromatograph through a silicone rubber septum. Two evacuated vessels and the flowmeter are slid into position, and the joints to the four-way stopcock are secured with springs.

The retention times of the samples were predetermined. The peaks were observed on the recorder during collection. Until the first sample eluted the effluent gas was allowed to escape through the flowmeter. Just before a sample was to elute a bubble was started in the flowmeter and the stopcock to one of the evacuated vessels opened and adjusted so that the bubble remained stationary in the flowmeter. In this way the effluent containing the total sample was collected without disturbing the pressure at the gas chromatography outlet. When the entire sample had been collected the vessel stopcock was turned to allow collection in the other evacuated vessel. Until the second sample eluted the effluent gas passed from the system through the flowmeter. When the second sample eluted, the stopcock to the second collection vessel was opened and adjusted as with the first sample.

IV Analysis of the Collected Sample

The vessel containing the sample and carrier gas was immersed in liquid nitrogen and cooled for 10 min. The stopcock was opened to a vacuum (0.5-2.0 mm.) for 10 min. and then closed. The vessel was allowed to warm to room temperature after attachment to the mass spectrometer, the stopcock was opened and the mass spectrum recorded.

V Results

A) Deuterium Exchanged 3-Methyl-2-butanone (III)[a2]

A 100-ml. flask was equipped with a magnetic stirrer and a reflux condenser with a drying tube. 3-Methyl-2-butanone (III) (8.61 g., 0.100 mole), deuterium oxide (20.0 g., 1.00 mole) and 2.0 g. of anhydrous potassium carbonate were added. This mixture was stirred for 4 hr. at 60°. The organic layer was separated, dried over sodium sulfate and filtered. Nmr ($CDCl_3$) δ1.04 (s, 100 mole %, $C(CH_3)_2$), 2.03 (s, 3.0 mole %, $CH_3$), 2.50 (m, 27.0 mole %, CH). The percent of total deuterium incorporated in ketone III[a2], as calculated by nmr, was 90.0%. 3-Methyl-2-butanone (III)[a2] was used without further purification.

B) Deuterated 3-Methyl-2-butanone (III)[a3]

3-Methyl-2-butanone (III)[a3] was prepared by mixing equal volumes of ketone III[a2] and undeuterated ketone III. Nmr ($CDCl_3$) δ1.06 (d, 100 mole %, $C(CH_3)_2$), 2.05 (s, 76.8 mole %, $CH_3$), 2.39 (m, 150.6 mole %, CH).

The percent of total deuterium incorporated in ketone III [a3] as calculated by nmr, was 44.2%.

C) Mass Spectral Comparison of Deuterated Samples:

1) Injected Directly into a Collection Vessel.

2) Collected from the Gas Chromatograph.

One sample of each ketone, III[a2] and III[a3], was injected directly into a collection vessel. Another sample of each ketone was chromatographed (Col. 3, 100°) and collected in an evacuated collection vessel. The contents of each collection vessel was analyzed by mass spectrometry using the complete procedure described on p. 140. The entire analysis was repeated three times.

VI Discussion

Table XVIII, p. 143, and Table XIX, p. 144, show the percent deuterium incorporation and isotopic distribution in ketones III[a2] and III[a3], respectively, collected from the gas chromatograph or injected directly into a collection vessel. In the cases of both ketone samples, the mass spectrum of collected or directly-injected samples are essentially identical. Furthermore, the values for the percent total deuterium incorporation in ketone III[a2] and III[a3], determined by mass spectrometry, agree with those determined by nmr.

These data indicate that the collection procedure does not alter the ratio of deuterated species present, and that 100% of each peak is successfully collected by the total collection system.

The total effluent gas chromatography collection system has been successfully used to analyze, for deuterium incorporation, samples in solution as dilute as 5%, which could not otherwise be isolated.

Table XVIII: Percent Deuterium Incorporation and Isotopic Distribution in 3-Methyl-2-butanone (III)[a2].

| | | Isotopic Distribution m/e - relative %[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | 86 | 87 | 88 | 89 | 90 | 91 |
| Entry | % Deuterium Incorporation | $d_0$ | $d_1$ | $d_2$ | $d_3$ | $d_4$ | $^{13}C$% |
| Injected | | | | | | | |
| scan 1 | 86.9 | 1.6 | 8.5 | 4.5 | 40.6 | 100.0 | 7.5 |
| scan 2 | 85.3 | 2.4 | 10.7 | 5.4 | 40.1 | 100.0 | 7.1 |
| scan 3 | 86.6 | 2.5 | 7.9 | 5.0 | 39.8 | 100.0 | 7.3 |
| | 86.3±1.0 | 2.2 ±0.4 | 9.0 ±1.1 | 5.0 ±0.3 | 40.2 ±0.3 | 100.0 | 7.3 ±0.1 |
| Collected | | | | | | | |
| scan 1 | 90.7 | <1 | 2.3 | 3.8 | 40.2 | 100.0 | 6.5 |
| scan 2 | 91.0 | <1 | 2.2 | 4.1 | 40.4 | 100.0 | 5.6 |
| scan 3 | 90.1 | <1 | 2.3 | 3.3 | 40.9 | 100.0 | 5.8 |
| | 90.6±0.5 | <1 | 2.3 ±0.0 | 3.7 ±0.3 | 40.5 ±0.3 | 100.0 | 6.0 ±0.4 |

[a]Corrected for (M+1) contribution.

Table XIX: Percent Deuterium Incorporation and Isotopic Distribution in 3-Methyl-2-butanone (III)[a3].

| Entry | % Deuterium Incorporation | | Isotopic Distribution m/e - relative %[a] 86 $d_0$ | 87 $d_1$ | 88 $d_2$ | 89 $d_3$ | 90 $d_4$ | 91 $^{13}C$% |
|---|---|---|---|---|---|---|---|---|
| Injected | | | | | | | | |
| scan 1 | 44.1 | 100.0 | | 0.2 | 2.9 | 26.0 | 64.1 | 6.4 |
| scan 2 | 43.8 | 100.0 | | 1.5 | 3.3 | 25.8 | 63.2 | 5.5 |
| scan 3 | 44.8 | 100.0 | | 1.1 | 2.8 | 26.7 | 66.6 | 5.8 |
| | 44.2±0.6 | 100.0 | | 0.9 ±0.5 | 3.0 ±0.2 | 26.2 ±0.4 | 64.6 ±1.3 | 5.7 ±0.3 |
| Collected | | | | | | | | |
| scan 1 | 45.1 | 100.0 | | 0.0 | 3.9 | 26.1 | 67.6 | 7.7 |
| scan 2 | 44.2 | 100.0 | | 1.7 | 2.5 | 27.6 | 64.3 | 5.5 |
| scan 3 | 44.2 | 100.0 | | 1.1 | 3.0 | 25.6 | 65.1 | 5.8 |
| | 44.5±0.6 | 100.0 | | 0.9 ±0.6 | 3.1 ±0.5 | 26.4 ±0.8 | 65.7 ±1.0 | 6.3 ±1.0 |

[a]Corrected for (M+1) contribution.

## References


1. A. Fischer and B. Winter, Monatch. Chem., 21, 30 (1900).

2. H. M. Gladstone, Ph.D. Dissertation, Polytechnical Institute of Brooklyn, (1961).

3. T. Yvernault and M. Mazet, Bull. Soc. Chim. France., 2755 (1967).

4. T. Yvernault and M. Mazet, Bull. Soc. Chim. France., 3352 (1968).

5. T. Yvernault and M. Mazet, Bull. Soc. Chim. France., 4309 (1969).

6. T. Yvernault and M. Mazet, Bull. Soc. Chim. France., 2652 (1971).

7. M. B. Green and W. J. Hickinbottom, J. Chem. Soc., 3262 (1957).

8. P. Demersman, J. Egged and R. Royer, Bull. Soc. Chim. France., 1364 (1974).

9. A. J. Kascheras, Ph.D. Dissertation, City University of New York, (1969).

10. D. M. Brouwer and J. A. Van Doorn, Rec. Trav. Chim. Pays-Bas., 90, 1011 (1971).

11. R. L. Baird and A. D. Aboderin, J. Amer. Chem. Soc., 86, 252 (1964).

12. C. C. Lee and L. Gruber, J. Amer. Chem. Soc., 90, 3775 (1968).

13. M. Saunders, P. Vogel, E. L. Hagen and J. Rosenfeld, Accts. Chem. Res., 6, 53 (1973).

14. N. C. Deno, W. E. Billups, D. La Vietes, P. C. Scholl, and S. Schneider, J. Amer. Chem. Soc., 92, 3700 (1970).

15. A. Fry in "Mechanisms of Molecular Migrations," Vol. 4, edited by B. S. Thyaragajan, John Wiley and Sons, Inc., New York, 1971, pp. 113 ff.

16. A. Fry, Private Communication.

17. C. H. Depuy and F. W. Bretbeil, J. Amer. Chem. Soc., 85, 2176 (1963).

18. M. Hanack and H. J. Schneider, Angew. Chem. Internat. Edn., 6, 666 (1967).

19. K. B. Wiberg, B. A. Hess, Jr. and A. J. Ashe in "Carbonium Ions," Vol. III, edited by G. A. Olah and P. v. R. Schleyer, Wiley Interscience, New York, 1972, pp. 1295 ff.

20. J. D. Roberts, E. F. Cox, M. C. Caserio and M. S. Silver, J. Amer. Chem. Soc., 83, 2179 (1961).

21. Z. Majerski and P. v. R. Schleyer, J. Amer. Chem. Soc., 93, 665 (1971).

22. R. M. Acheson, Accts. Chem. Res., 4, 177 (1971).

23. R. N. McDonald in "Mechanisms of Molecular Migrations," Vol. 3, edited by B. S. Thyarагajan, John Wiley and Sons, Inc., New York, 1971, pp. 67 ff.

24. J. Kagan and J. T. Przybytek, Tetrahedron, 29, 1163 (1973).

25. J. D. Roberts and R. H. Mazur, J. Amer. Chem. Soc., 73, 2509 (1951).

26. E. Renk and J. D. Roberts, J. Amer. Chem. Soc., 83, 878 (1961).

27. M. C. Caserio, W. H. Graham and J. D. Roberts, Tetrahedron, 11, 171 (1960).

28. C. G. Bergstrom and S. Siegal, J. Amer. Chem. Soc., 74, 145 (1952).

29. R. H. Mazur, W. N. White, D. A. Semenew, C. C. Lee, M. S. Silver and J. D. Roberts, J. Amer. Chem. Soc., 81, 4390 (1959).

30. J. E. Baldwin and W. D. Foglesong, J. Amer. Chem. Soc., 90, 4303 (1968).

31. P. v. R. Schleyer and G. W. Van Dine, J. Amer. Chem. Soc., 88, 2321 (1966).

32. G. A. Olah, C. L. Jevell, D. P. Kelley and R. D. Porter, J. Amer. Chem. Soc., 94, 146 (1972).

33. M. Saunders and J. Rosenfeld, J. Amer. Chem. Soc., 92, 2548 (1970).

34. E. R. Alexander and D. C. Dittmer, J. Amer. Chem. Soc., 73, 1665 (1951).

35. D. J. Cram, J. Amer. Chem. Soc., 74, 2137 (1952).

36. J. N. Marx, J. C. Argyle and L. R. Norman, J. Amer. Chem. Soc., 96, 2121 (1974).

37. L. P. Hammett and H. J. Deyrup, J. Amer. Chem. Soc., 54, 2721 (1932).

38. J. Sierra, M. Ojeda and P. A. H. Wyatt, J. Chem. Soc., B, 1570 (1970).

39. M. J. Jorgenson and D. R. Harrter, J. Amer. Chem. Soc., 85, 878 (1963).

40. C. G. Malmberg, J. Res. Natl. Bur. Stand., 60, 609 (1958).

41. K. F. Bonhoeffer and O. Reitz, Z. Phys. Chem. Abt. A., 179, 135 (1937).

42. E. Hogfeldt and J. Bigelsisen, J. Amer. Chem. Soc., 82, 15 (1960).

43. M. Liler, "Reaction Mechanisms in Sulfuric Acid," Academic Press, New York, 1971, p. 168.

44. J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co. Inc., New York, 1962, p. 120.

45. C. C. Lee, A. J. Cessna, E. C. Ko and S. Vassie, J. Amer. Chem. Soc., 95, 5568 (1973).

46. P. C. Hariharan, L. Radom, J. A. Pople and P. v. R. Schleyer, J. Amer. Chem. Soc., 96, 599 (1974).

47. N. Bodor and M. J. S. Dewar, J. Amer. Chem. Soc., 94, 5303 (1972).

48. G. S. Hammond, J. Amer. Chem. Soc., 77, 334 (1955).

49. Reference 43, p. 25.

50. L. Thorne, Proc. Chem. Soc., 39, 543 (1881).

51. N. Weiner in "Organic Synthesis," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, 1943, p. 280.

52. E. Testa and L. Fontella, J. Org. Chem., 24, 1932 (1959).

53. R. W. Shortridge, R. A. Craig, K. W. Greenlee, J. M. Derfer, and C. E. Boord, J. Amer. Chem. Soc., 70, 946 (1948).

54. E. Champiagnone and W. M. LeSeur in "Organic Synthesis," Coll. Vol. IV, N. Rabjohn, ed., John Wiley and Sons, Inc., New York, 1963, pp. 919 ff.

55. T. W. Mears, A. Fookson, P. Pomerantz, E. H. Rich, C. S. Dussinger and F. L. Howard, J. Res. Natl. Bus. Stand., 44, 299 (1950).

56. R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, 1948, p. 253.

57. I. Heilbron, "Dictionary of Organic Compounds," Vol. III, Oxford University Press, New York, 1953 p. 477.

58. J. D. Roberts and J. Yancey, J. Amer. Chem. Soc., 77, 5558 (1955).

59. I. Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, 1953, p. 428.

60. W. Judefind and E. E. Reid, J. Amer. Chem. Soc., 42, 1043 (1920).

61. M. Oka and A. Fry, J. Org. Chem., 8, 2801 (1970).

62. G. B. Malone and E. E. Reid, J. Amer. Chem. Soc., 51, 3424 (1929).

63. C. C. Lee, J. Clayton, D. Lee and A. Finlayson, Tetrahedron, 18, 1395 (1962).

64. K. Folkers and H. Adkins, J. Amer. Chem. Soc., 53, 1416 (1931).

65. I. Heilbron, "Dictionary of Organic Compounds," Vol. III, Oxford University Press, New York, 1953, p. 286.

66. D. Chang, S. Lee, J. Org. Chem., 32, 3716 (1967).

67. E. Jenny and J. D. Roberts, J. Amer. Chem. Soc., 78, 2008 (1956).

68. P. A. T. Swoboda, Nature, 31 (1963).

69. S. Dal Nogare and R. S. Juvet Jr., "Gas Liquid Chromatography," Interscience, New York-London, 1962, p. 253.

70. S. Dal Nogare and L. W. Safranski in "Organic Analysis," Vol. IV, J. Mitchell Jr., ed., Interscience, New York-London, 1960, p. 182.