THE ACID CATALYZED REARRANGEMENTS OF 2,2-DIALKYL-1,3-PROPANEDIOLS AND RELATED COMPOUNDS

by

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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.

1969

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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ACKNOWLEDGEMENTS

The author wishes to express his appreciation to Professor Leonard H. Schwartz for his continual guidance, encouragement, and patience throughout this research.

The author also wishes to thank Dr. Peter Butler for the furnishing of a great deal of the mass spectral data compiled in this dissertation, and Mr. James Buell for the courage and kindness expressed during the formulation of this thesis.

The author acknowledges financial support in the form of a National Science Foundation Graduate Traineeship (1966-1968).

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INTRODUCTION

The unambiguous confirmation of 1,3-hydride shift pathways in carbonium ion reactions has been the concern of many investigators recently. Reutov[1] observed that the nitrous acid deamination of the perchlorate salt of 1-propylamine-1-C^{14} resulted in the formation of C-1 and C-3 labeled 1-propanol, in addition to labeled 2-propanol. A 1,3-hydride shift pathway (eq 1) was suggested. A route involving two 1,2-hydride shifts (eq 2) was not ruled out.

These results exclude methyl migration (eq 3), which would result in C-2 labeled 1-propanol.

Karabatsos[2] verified Reutov's supposition that a 1,3-hydride shift had occurred by considering the nitrous acid deamination of 1,1,2,2-tetradeuterio-1-propylamine.

Nmr analysis of the 1-propanol fraction allowed the presence of (I) (eq 4) to be established to the extent of 11.8% (a reinvestigation of the problem, taking advantage of mass spectral analysis of the trimethylsilyl ether derivatives, reduced this value to 5.0%[3]). Further evidence against the pathway involving two 1,2-hydride shifts (eq 5) was secured when 2-propylamine was found to yield 2-propanol without a trace of 1-propanol.

In addition to the above observations, the observation was made that cyclopropane was formed in the deamination of propylamine,[4] and

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(1) O. A. Reutov and T. N. Shatkina, Tetrahedron, 18, 237 (1962)

(2) G J Karabatsos and C. E. Orzech, Jr., J. Amer. Chem. Soc. 84, 2838 (1962).

(3) G. J. Karabatsos and S. Meyerson, ibid., 87, 4394 (1965).

(4) P. S. Skell and I. Starer, ibid., 82, 2971 (1960).

$$\begin{array}{l} \qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3\text{-}CH_2\text{-}C^{14}H_2OH \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad H_2O \uparrow \\ CH_3\text{-}CH_2\text{-}C^{14}H_2\text{-}NH_2 \xrightarrow{HNO_2} CH_3\text{-}CH_2\text{-}C^{14}H_2^+ \xrightarrow{1,3\text{-}H\sim} \\ +CH_2\text{-}CH_2\text{-}C^{14}H_3 \xrightarrow{H_2O} HOCH_2\text{-}CH_2\text{-}C^{14}H_3 \end{array} \qquad (1)$$

$$\begin{array}{l} \qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3\text{-}CH_2\text{-}C^{14}H_2OH \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad H_2O \uparrow \\ CH_3\text{-}CH_2\text{-}C^{14}H_2\text{-}NH_2 \xrightarrow{HNO_2} CH_3\text{-}CH_2\text{-}C^{14}H_2^+ \underset{}{\overset{1,2\text{-}H\sim}{\rightleftharpoons}} \\ CH_3\text{-}\overset{+}{C}H\text{-}C^{14}H_3 \underset{1,2\text{-}H\sim}{\rightleftharpoons} +CH_2\text{-}CH_2\text{-}C^{14}H_3 \xrightarrow{H_2O} HOCH_2\text{-}CH_2\text{-}C^{14}H_3 \end{array} \qquad (2)$$

$$CH_3\text{-}CH_2\text{-}C^{14}H_2^+ \longrightarrow \left[\begin{array}{c} CH_3 \\ \diagup\ \overset{+}{}\ \diagdown \\ CH_2 \text{---} C^{14}H_2 \end{array}\right] \longrightarrow +CH_2\text{-}C^{14}H_2\text{-}CH_3 \qquad (3)$$

$$\begin{array}{l} CH_3\text{-}CD_2\text{-}CD_2\text{-}NH_2 \xrightarrow{HNO_2} CH_3\text{-}CD_2\text{-}CD_2^+ \xrightarrow{1,3\text{-}H\sim} \\ \qquad +CH_2\text{-}CD_2\text{-}CHD_2 \xrightarrow{H_2O} HOCH_2\text{-}CD_2\text{-}CHD_2 \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad \text{I} \end{array} \qquad (4)$$

$$\begin{array}{l} CH_3\text{-}CD_2\text{-}CD_2\text{-}NH_2 \xrightarrow{HNO_2} CH_3\text{-}CD_2\text{-}CD_2^+ \underset{}{\overset{1,2\text{-}H\sim}{\rightleftharpoons}} \\ CH_3\text{-}\overset{+}{C}D\text{-}CD_3 \underset{1,2\text{-}H\sim}{\rightleftharpoons} +CH_2\text{-}CHD\text{-}CD_3 \xrightarrow{H_2O} HOCH_2\text{-}CHD\text{-}CD_3 \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad \text{II} \end{array} \qquad (5)$$

in the "deoxideation" of 1-propanol.[5] As a result, a protonated cyclopropane of structure (III) and structure (IV) were suggested as possible intermediates. An investigation of the solvolysis of cyclopropane in 8.43 M deuteriosulfuric acid[6] gave the average deuterium distribution in the 1-, 2-, and 3-positions of the 1-propanol fraction as 0.38, 0.17, and 0.46 deuterium atom, respectively. These results were interpreted in terms of a hydrogen-bridged intermediate (V). More recently, however, Deno[7] has reported that the 1-propyl hydrogen sulfate resulting from passage of cyclopropane through deuteriosulfuric acid of various concentrations showed an equal distribution of deuterium at each of the three carbon positions. Accordingly, participation by a protonated cyclopropane of structure (III) cannot be excluded, and, indeed, since it has been suggested that all of these intermediates would be of approximately the same energy,[8] a more correct picture might include all of the above. A study in tritiated sulfuric acid[9] gave results which might be regarded as in better agreement with the observations of Baird.

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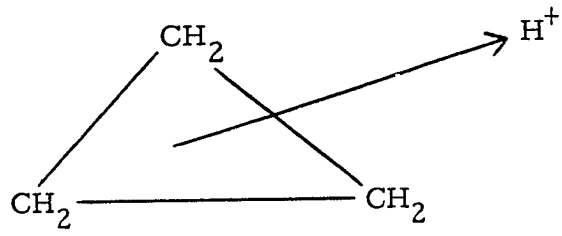
(5) P. S. Skell and I. Starer, ibid., 84, 3962 (1962).

(6) R. L. Baird and A. A. Aboderin, ibid., 86, 252 (1964).

(7) N. C. Deno, D. Lavietes, J. Mockus, and P. C. Scholl, ibid., 90, 6457 (1968).

(8) N. C. Deno, lecture given at the 152nd National Meeting of the American Chemical Society, New York, N.Y., Sept. 12-16, 1966.

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



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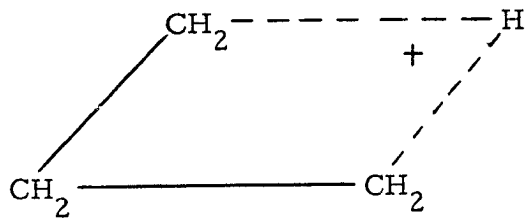

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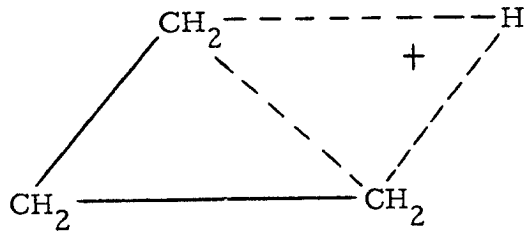
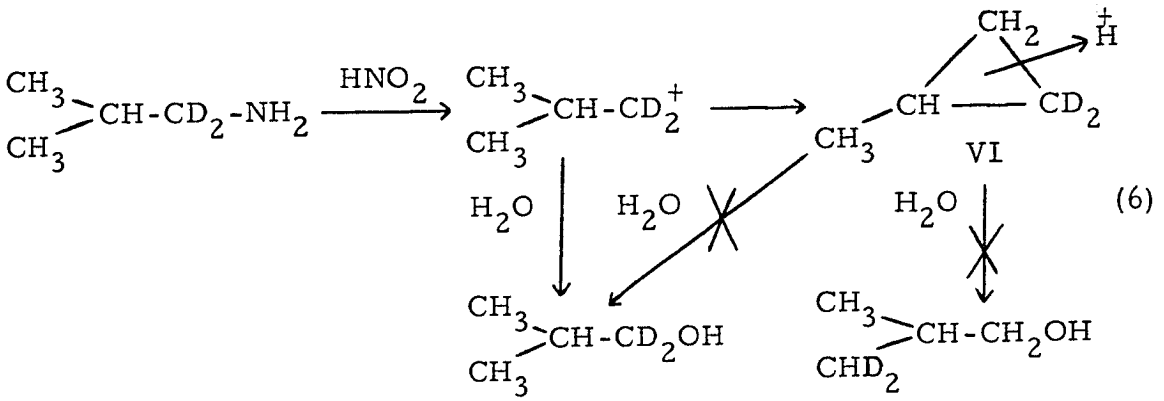


V

Under deamination conditions isobutylamine gives some methylcyclopropane.[10] Assessment of the isotope-position distribution in the isobutyl alcohol obtained from the deamination[11] of isobutylamine-1,1-d_2 failed to demonstrate the presence of (VI), as only isotopically unrearranged alcohol was obtained (eq 6).



(6)

(VI), if present, can be detected only by formation of methylcyclopropane.

In contrast, neopentylamine gives no dimethylcyclopropane.[12] The deamination of neopentyl-1-^{13}C and neopentyl-1,1-d_2-amines, and the solvolysis of neopentyl-1-^{13}C and neopentyl-1,1-d_2-tosylates[13] produced t-amyl derivatives in which the label originally at C-1 in the neopentyl compound was found only at C-3 in the t-amyl compound. Since 1,2-methyl shifts could entirely account for these observations,

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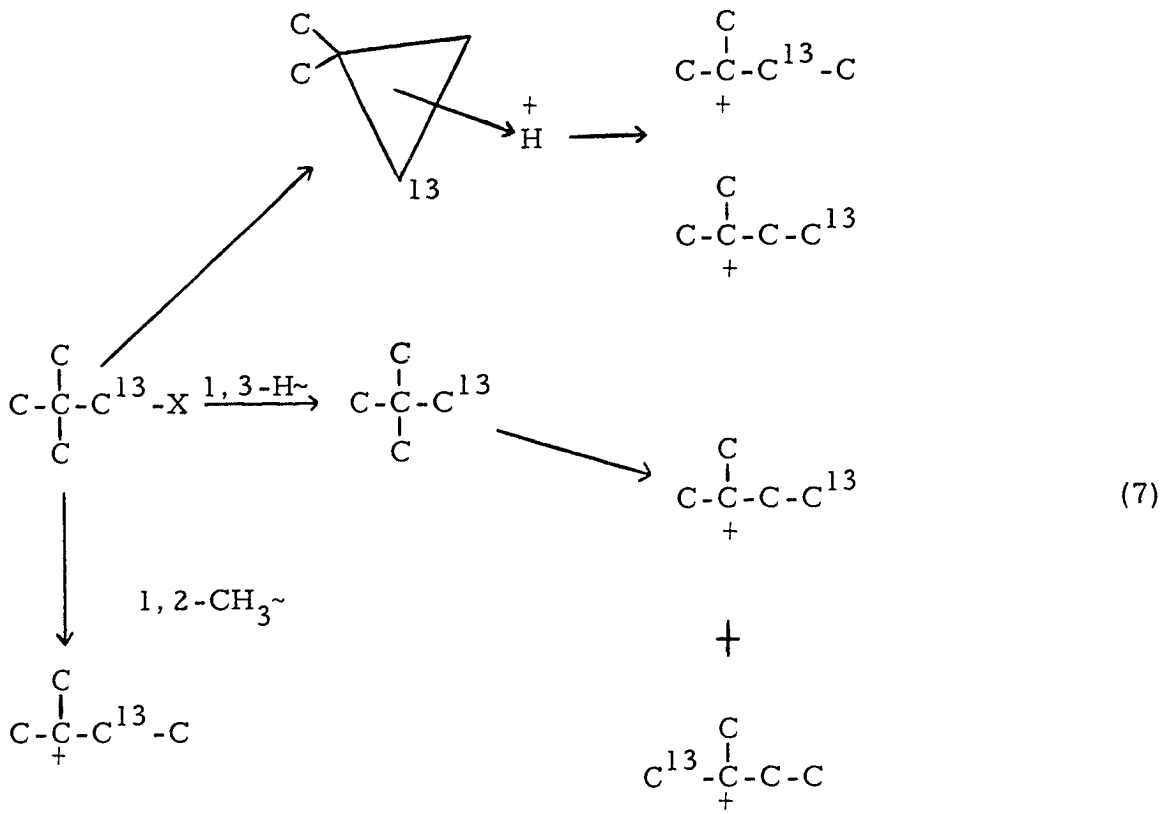
(10) M. S. Silver, ibid., 82, 2971 (1960).

(11) G. J. Karabatsos, N. Hsi, and S. Meyerson, ibid., 88, 5649 (1966).

(12) J. H. Bayless, F. D. Mendicino, and L. Friedman, ibid., 87, 5790 (1965).

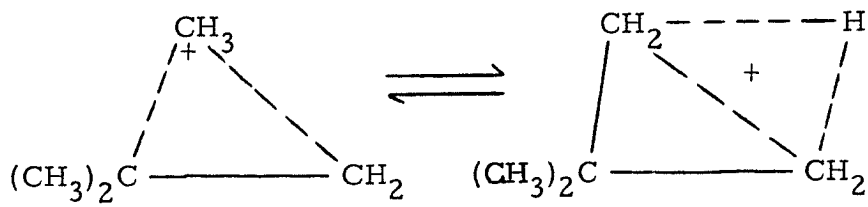
(13) G. J. Karabatsos, C. E. Orzech, Jr., and S. Meyerson, ibid., 86, 1994 (1964).

the conclusion was drawn that neopentyl compounds rearrange to t-amyl compounds without the intervention of 1,3-hydride shifts, protonated cyclopropanes, or hydrogen bridged ions (eq 7). Apparently, the methyl



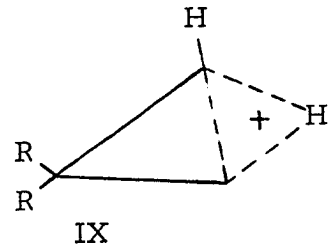
(7)

shift intermediate (VII), rearranges to the very stable tertiary t-amyl cation much faster than it equilibrates with (VIII) or forms 1,1-dimethyl-cyclopropane. Another factor that might hinder equilibration of (VII) with



VII VIII

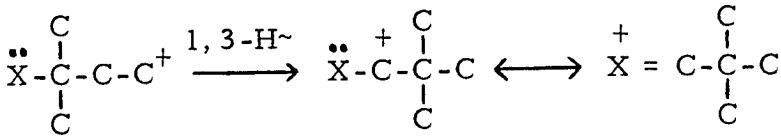
(VIII) is the 1,2-eclipsing interaction (IX) in (VIII).[13] This effect would be



IX

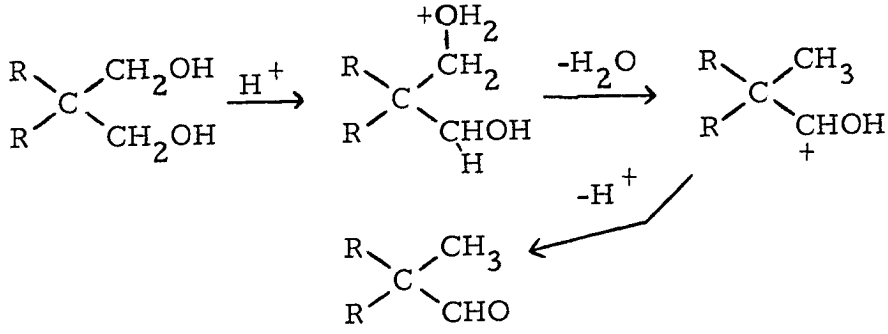
present to the least extent in the n-propyl system, and to an intermediate extent in the isobutyl system.

It is conceivable that a 1,3-hydride shift pathway could be encouraged in the neopentyl system if the resultant carbonium ion were stabilized by a substituent containing unshared electron pairs (eq 8).



(8)

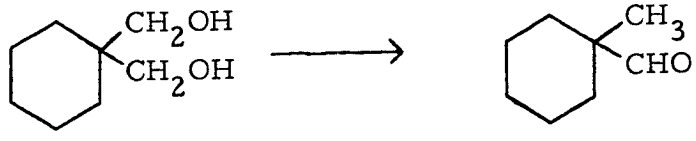
It has been reported[14] that the sulfuric acid-catalyzed rearrangements of 2,2-dialkyl-1,3-propanediols do not yield products which are consistent with a 1,3-hydride shift from the methylol group (eq 9). If the



(9)

(14) H. M. Gladstone, Ph.D. Thesis, Polytechnic Institute of Brooklyn, 1961.

assumption is made that the reactivities of the tertiary aldehydes would not preclude their isolation, the absence of such products rule out a 1, 3-hydride shift mechanism. A more recent investigation[15] of the rearrangement products from 1, 1-bis-(hydroxymethyl)cyclohexane has demonstrated the presence of α-methylcyclohexanecarboxaldehyde, the expected product of a 1, 3-hydride shift.



In the light of this result, it was of interest to investigate the sulfuric acid-catalyzed rearrangements of the simplest member of the family of 2, 2-dialkyl-1, 3-propanediols, 2, 2-dimethyl-1, 3-propanediol, as well as the more complex 1, 1-bis-(hydroxymethyl)cyclohexane. Direct dehydration in these systems is not possible, as they lack an alpha hydrogen. Therefore, carbon skeletal rearrangement was to be expected. It was hoped that deuterium labeling, in conjunction with nmr and mass spectral analysis of the products, would shed light on the mechanism of formation of rearrangement products.

The acid catalyzed rearrangements of 2, 2-disubstituted-1, 3-propanediols have been studied previously.[14, 16] However, these investigations were concerned primarily with the kinetic aspects of the

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(15) L. H. Schwartz, unpublished results.

(16) T. Yvernautt and N. Mazet, Bull. Soc. Chim. France, 2755 (1967).

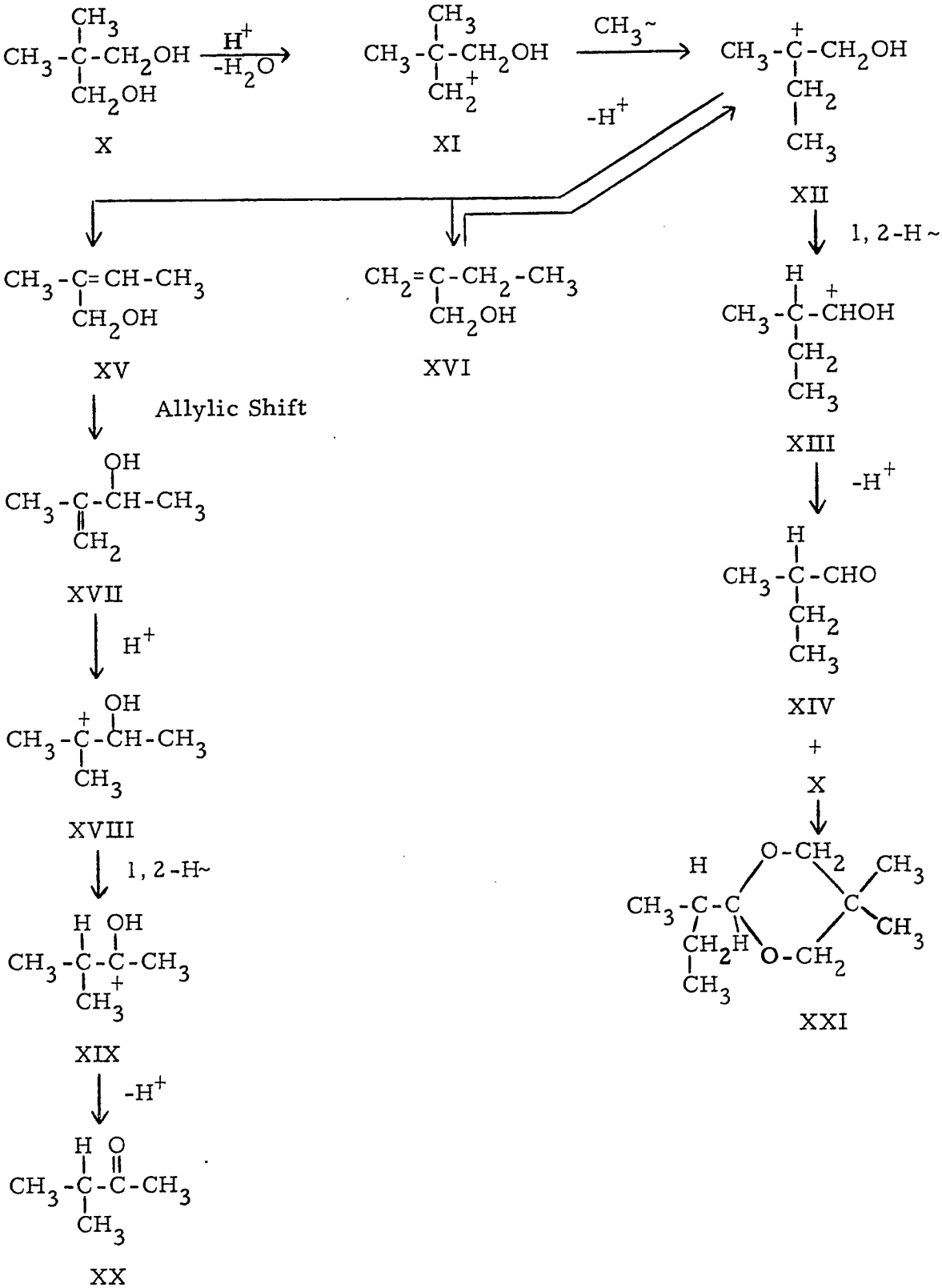
reactions, rather than with mechanistic considerations. Thus, the dilute sulfuric acid reaction of 2,2-dimethyl-1,3-propanediol was reported to yield three major products: 2-methylbutyraldehyde (XIV), methyl isopropyl ketone (XX), and 5,5-dimethyl-2-(2-butyl)-1,3-dioxane (XXI). In order to account for these transformations, an allylic shift pathway was assumed (Mechanism I), although no experimental evidence, such as that which might be obtained from deuterium-labeled systems, was presented.

In this dissertation, two systems will be considered:

System I; the reaction of a 1,1,3,3-tetradeuterio-labeled propanediol with sulfuric acid.

System II; the reaction of an unlabeled propanediol with deuteriosulfuric acid.

MECHANISM I



RESULTS AND DISCUSSION

(A) The Rearrangement of 2, 2-Dimethyl-1, 3-propanediol

(1) Results and Discussion of System I

The dropwise addition of an aqueous solution of 2, 2-dimethyl-1, -1, 3, 3-tetradeuterio-1, 3-propanediol (Xa) to a 50% sulfuric acid solution at 160°, while steam distilling volatile products via a vigorous stream of nitrogen, results in the formation of the above-mentioned products: 2-methylbutyraldehyde (XIV), methyl isopropyl ketone (XX), and 5, 5-dimethyl-2-(2-butyl)-1, 3-dioxane (XXI), separated by gas chromatography. The isotopic distribution of the 2-methylbutyraldehyde (XIV), as indicated by mass spectral analysis, is presented in Table I. Clearly, the major contribution is that of d_2 and d_3 content. Nmr analysis reveals a methyl quintet (J = 2 cps) indicating a CH_3-CD_2- grouping. Integration of the aldehyde-H here shows approximately 40% -CHO. These observations are consistent with a 1, 2-methyl shift pathway for formation of the aldehyde, as shown in Mechanism II, where steps (XIIa)⟶(XIIIa)⟶(XIVa) are reversible.

The isotopic distribution of the ketone (XX) as determined by mass spectrometry is as follows: 58.3% d_0, 19.2% d_1, 21.9% d_2, 0.4% d_3. The presence of d_0, d_1, and d_2 compounds is consistent with mechanism II. The large d_0 value could, in the absence of data soon to be considered in system II, be attributed to either the reversibility of step (XVIIa)⟶(XVIIIa) or proton exchange in the ketone product itself.

TABLE I

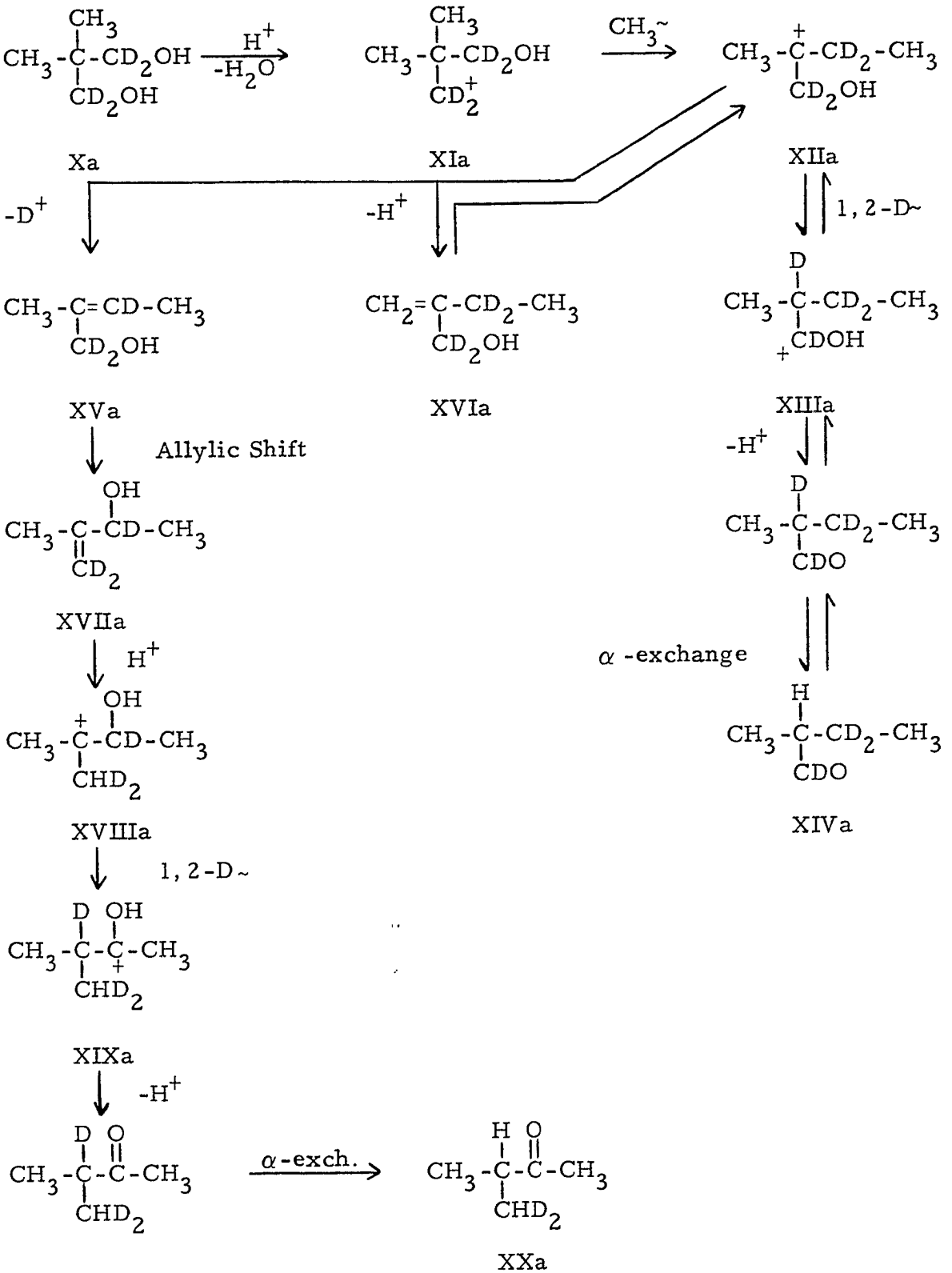
Isotopic Distribution of 2-Methylbutyraldehyde[a]

m/e (%)

Reactant	86	87	88	89	90
	d_0	d_1	d_2	d_3	d_4
$(CH_3)_2C(CD_2OH)_2$ + H_2SO_4	2.7	9.0	51.3	35.3	1.7
$(CH_3)_2C(CH_2OH)_2$ + D_2SO_4	15.5	45.8	30.8	6.0	1.9
$CH_3-CH_2-C(H)(CH_3)-CHO$ + D_2SO_4	12.4	28.6	51.3	6.9	0.8
$HOCH_2-C(CH_3)(OH)-CH_2-CH_3$ + D_2SO_4	11.3	52.1	29.9	5.7	1.0

(a) Corrected for (M+1) contribution, but not for (M-1) which is 4.1% of M in unlabeled 2-methylbutyraldehyde.

MECHANISM II



(2) Results and Discussion of System II

The addition of a deuterium oxide solution of 2, 2-dimethyl-1, 3-propanediol to deuteriosulfuric acid (system II) in a manner analogous to that described for system I, gave a product distribution similar to that of system I.

The 2-methylbutyraldehyde formed was composed mainly of d_1 and d_2 species (Table I). NMR analysis indicated no α-hydrogen and approximately 60% -CDO. These results are compatible with those from system I, whereby formation of aldehyde occurs via a 1, 2-methyl shift pathway with steps (XIIb)$\rightarrow$ (XIIIb)$\rightarrow$ (XIVb) being reversible (see Mechanism III, page 19). This reversibility can be further substantiated by considering the behavior of 2-methylbutyraldehyde itself under the deuteriosulfuric acid reaction conditions. The reaction results in formation of methyl isopropyl ketone and recovery of 2-methylbutyraldehyde. The recovered aldehyde (Table I) consisted predominately of d_1 and d_2 species. Nmr spectroscopy again indicated the deuterium to be on the α-carbon and partially on the aldehyde carbon.

In an attempt to demonstrate the intermediacy of (XIIb), 2-methyl-1, 2-butanediol was subjected to reaction in deuteriosulfuric acid. The same aldehyde (XIV) and ketone (XX) were again obtained, in a ratio of approximately 2:1. If (XIIb) were a common intermediate for formation of both aldehyde and ketone, the ratio of products here should be equal to that from the 2, 2-dimethyl-1, 3-propanediol. The ratio of aldehyde to ketone from the latter is approximately 3:2. The added complication of acetal formation in this case makes ratio comparison difficult. The

2-methylbutyraldehyde (XIV) from the 2-methyl-1, 2-butanediol reaction contained mostly d_1 and d_2 species (Table I). Nmr analysis showed the absence of alpha hydrogen and the incorporation of approximately 60% -CDO.

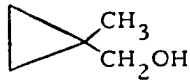
Based on the above results, a conclusion can now be drawn concerning formation of 2-methylbutyraldehyde (XIV) from the reaction of 2, 2-dimethyl-1, 3-propanediol with 50% sulfuric acid at 160°. Such formation takes place via a 1, 2-methyl shift pathway (Mechanism I, page 11), with steps (XII)→(XIII)→(XIV) being reversible.

The methyl isopropyl ketone from the reaction of 2, 2-dimethyl-1, 3-propanediol with deuteriosulfuric acid shows a wide spectrum of isotopic distribution (Table II). The major contributions are the d_5, d_6, d_7 and d_{10} components. An allylic shift pathway, as shown in Mechanism III, page 19, predicts the incorporation of five deuterium atoms into the ketone (XXb). This assumes the ready exchangeability of the four alpha hydrogens of the system. This was tested by subjecting methyl isopropyl ketone itself to the reaction conditions with D_2SO_4. The only material isolated was recovered methyl isopropyl ketone, which was shown by nmr analysis to contain no alpha hydrogen. Mass spectral analysis (Table II) indicated the predominance of a d_4 species. This data demonstrates both the alpha hydrogen exchangeability and the stability of the ketone product towards further deuteration at other than the α-positions under the reaction conditions. Since the ketone (XX) formed in the diol reaction is shown by nmr to be devoid of alpha hydrogens, the presence of a d_5 species is consistent with Mechanism III.

TABLE II

Isotopic Distribution of Methyl Isopropyl Ketone from D_2SO_4 Reactions [d]

m/e %

Reactant		86	87	88	89	90	91	92	93	94	95	96
		d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}
$(CH_3)_2C(CH_2OH)_2$ X	a—	0.8	0.3	0.5	0.6	5.2	32.4	19.1	16.3	3.7	3.9	16.6
	b—	0	0	0.8	6.0	4.0	23.3	17.7	20.3	5.4	5.8	22.1
	c—	0.2	0.1	0.2	0.5	4.0	17.5	15.3	24.8	6.4	7.3	23.7
$CH_3CH_2CH(CH_3)CHO$ XIV		0.9	1.7	2.8	1.3	2.9	5.9	20.6	31.2	6.4	7.8	18.5
$CH_3CH{=}C(CH_3)CH_2OH$ XV		1.5	1.7	1.3	1.3	6.9	75.4	3.5	1.7	1.0	0.9	4.8
		1.3	1.4	1.2	1.2	6.7	74.5	3.5	2.5	1.2	1.1	5.4
$CH_3CH(OH)C(CH_3){=}CH_2$ XVII		0.3	1.3	1.3	1.9	11.7	75.5	2.4	1.3	0.6	0.9	2.8
		1.0	1.2	0.9	1.2	8.1	78.0	3.1	1.5	0.8	0.8	3.4
$(CH_3)_2CHCOCH_3$ XX		0.7	1.4	2.1	4.7	90.3	0	0.1	0.7	0	0	0
$(CH_3)_3CCHO$ XXIII		0.4	0.6	1.2	4.4	90.3	1.4	0.2	0.3	0.2	0.2	0.8
 XXV		0	0	0	0	0.1	0.3	0.9	2.7	8.5	24.5	63.0
		0	0	0	0	0	0.3	1.0	2.4	7.7	20.0	68.6
		0	0	0	0	0	0.4	1.1	2.8	8.7	24.5	62.5
$CH_2{=}C(CH_3)CH_2CH_2OH$ XXXII		0	0	0	0	0.2	0.7	2.7	4.9	9.4	20.6	61.5
$CH_3CH_2C(OH)(CH_3)CH_2OH$ XXXIX		0.1	0.8	1.1	1.6	5.6	29.4	16.2	23.8	4.4	3.2	13.8

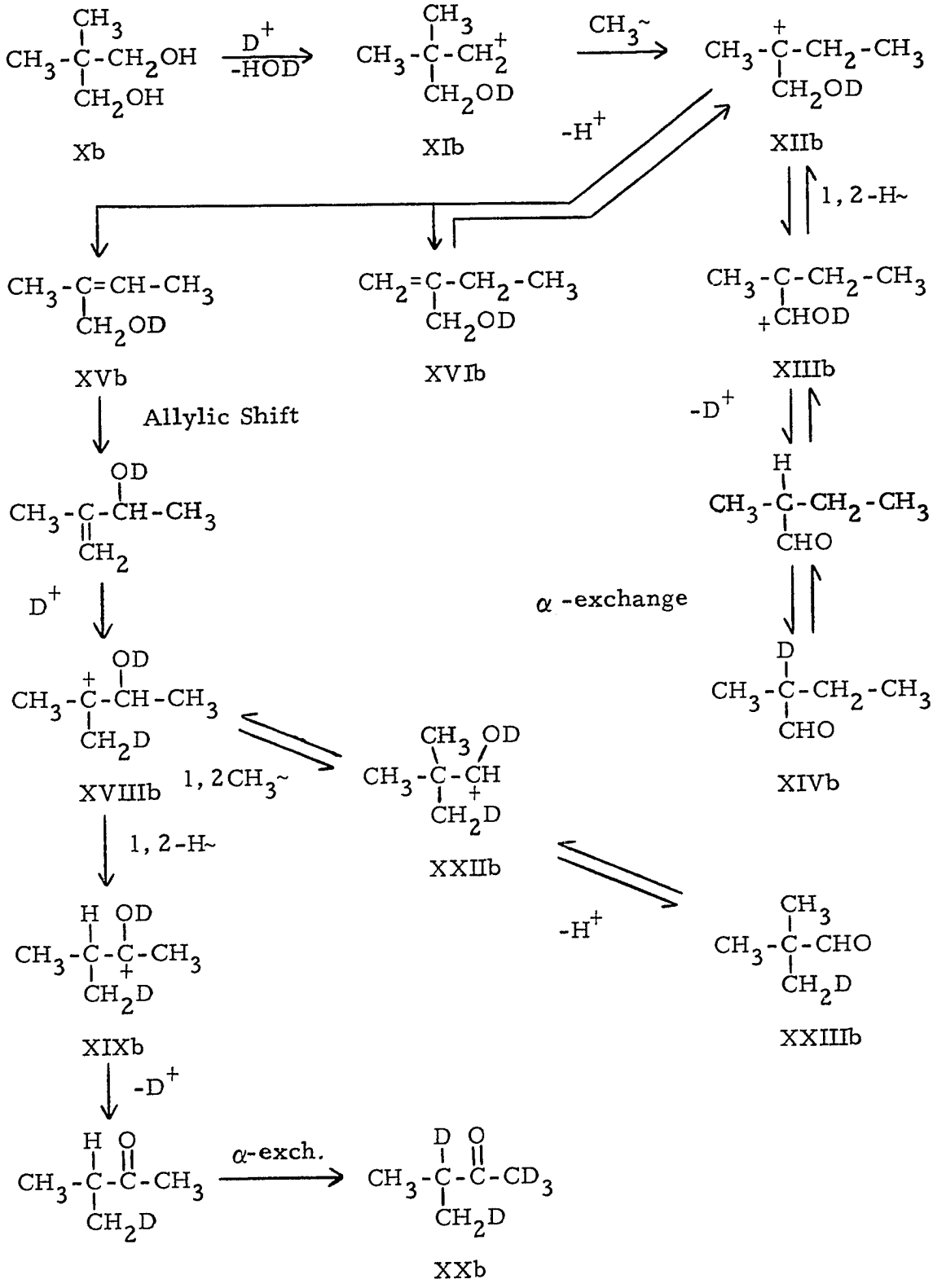
(a) Vigorous nitrogen flow employed, D_2O added after addition of diol soln. to sustain reaction.

(b) Nitrogen flow cut to 1/2 above value, D_2O added as above.

(c) Nitrogen flow as in (b), no D_2O added.

(d) Values corrected for (M + 1) contribution.

MECHANISM III



The presence of d_6 and d_7 species can be accounted for by invoking the previously demonstrated reversibility of steps (XIIb) ⟶ (XIIIb) ⟶ (XIVb) (p 16). The isotopic distribution above d_7 is indeed surprising. A minor contribution is made by the d_8 and d_9 species, while the d_{10} component is major. Mechanism III could accommodate this observation, provided step (XVIIb) ⟶ (XVIIIb) were reversible. This possibility suggested a consideration of the behaviors of 3-methyl-3-buten-2-ol (XVII) and 2-methyl-2-buten-1-ol (XV) under the reaction conditions. Hickenbottom[17] has reported the formation of methyl isopropyl ketone (XX) (63%) and 2-methylbutyraldehyde (XIV) (25%) from 2-methyl-2-buten-1-ol (XV) by treatment with dilute acid and Kondakov[18] has reported the formation of methyl isopropyl ketone (XX) exclusively, under similar conditions, from 3-methyl-3-buten-2-ol (XVII). When an aqueous solution of either allylic alcohol is added to a 50% sulfuric acid solution at 160° as described above (p 13), both methyl isopropyl ketone (XX) (90%) and 2-methylbutyraldehyde (XIV) (10%) are formed. With deuteriosulfuric acid (p 16), a similar distribution of ketone and aldehyde is observed. The ketone fraction is composed mainly of a d_5 species (Table II). Nmr analysis reveals no alpha hydrogen. These results are consistent with a non-reversible step (XVIIb) ⟶ (XVIIIb) in formation of the ketone (XXb). In addition to the aldehyde (XIV) and ketone (XX) products, a small amount of

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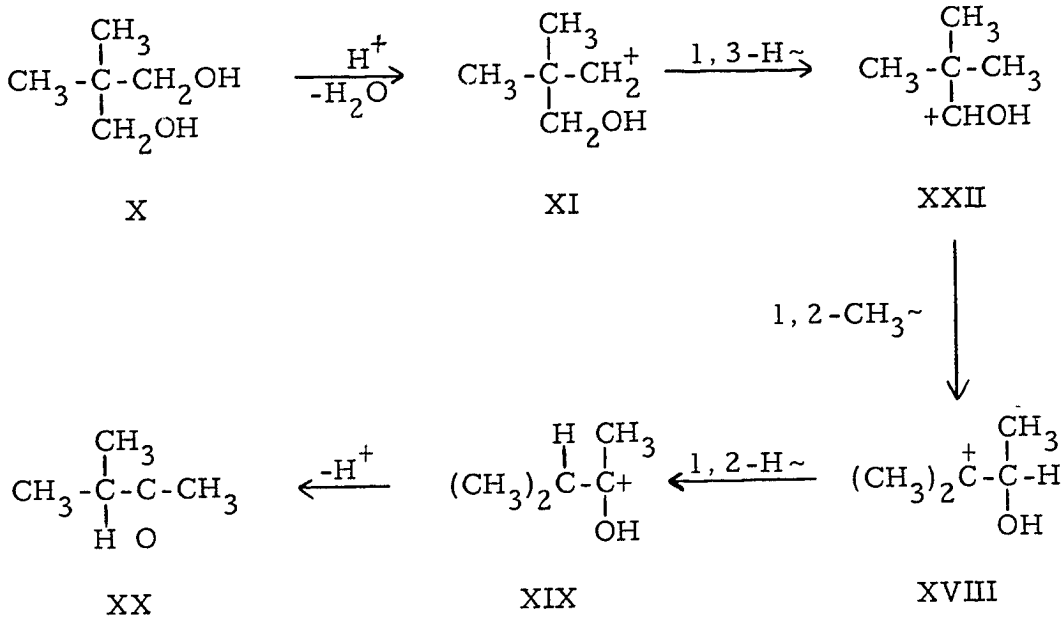
(17) W. J. Hickinbottom, J. Chem. Soc., 3262 (1957).

(18) R. Kondakov, J. Russ. Phys. Chem. Soc., 17, 290 (1885).

pivaldehyde (XXIIIb) is observed, which could account for the approximately 10% d_4 contribution. The protonated aldehyde (XXIIb) has presumably three methyl groups capable of migrating to form (XX). Migration of the mono-deuteriomethyl group created in step (XVIIb) ⟶ (XVIIIb) would lead eventually to a d_4 ketone, deuterated only in the α-positions. The presence of a significant amount of d_{10} contribution thus eliminates Mechanism III as the sole source of methyl isopropyl ketone (XX) from 2, 2-dimethyl-1, 3-propanediol (X). The observed incorporation of five deuterium atoms into the ketone (XX) from allylic alcohols (XV) and (XVII), coupled with the aforementioned reversibility of steps (XIIb) ⟶ (XIIIb) ⟶ (XIVb) in the aldehyde pathway, suggests the involvement of Mechanism III in formation of the d_5, d_6 and d_7 ketones (XX). The minimum found at d_8 and d_9 suggests the simultaneous operation of two mechanisms, one giving a mixture of d_5, d_6, and d_7 ketones (XX) (Mechanism III, p 19), and the other giving a d_{10} ketone (XX).

The possible intervention of a 1, 3-hydride shift pathway (Mechanism IV, p 22) in the formation of methyl isopropyl ketone (XX) from 2, 2-dimethyl-1, 3-propanediol (X) under acidic conditions has been considered previously.[15] The immediate product of such a shift would be protonated pivaldehyde (XXII). Pivaldehyde (XXIII) has been shown to rearrange to methyl isopropyl ketone (XX) under acidic conditions. However, since pivaldehyde has never been found among the reaction products from 2, 2-dimethyl-1, 3-propanediol (X), this pathway did not meet with favor and the allylic pathway (Mechanism I)

MECHANISM IV



was preferred.[15] The results of the present investigation are in agreement with those previously reported concerning the observed products from the acid catalyzed rearrangement of 2, 2-dimethyl-1, 3-propanediol. However, this investigation has revealed the formation of pivaldehyde (XXIII) from the allylic alcohol intermediates (XV and XVII) of Mechanism III (p 19). As a result, steps (XVIIIb) ⟶ (XXIIb) ⟶ (XXIIIb) have been included. Since evidence has been presented for the participation of Mechanism III in the formation of ketone (XX) from 2, 2-dimethyl-1, 3-propanediol (X) (p 21), the fact that (X) does not give pivaldehyde (XXIII) suggests that an equilibrium exists among (XVIIIb), (XXIIb), and (XXIIIb), and when (XVIIIb) is

generated in large amount, as is the case when precursors (XV) and (XVII) are employed, this equilibrium is shifted towards (XXIIb), whereby a trace of pivaldehyde (XXIIIb) is liberated. The consequence of such an equilibrium in Mechanism IV as the only pathway to (XVIII) would not be the same, inasmuch as (XVIII) must come from (XXII) in this case. Although it is not likely that (XXII) rearranged totally to (XVIII), without forming a trace of pivaldehyde (XXIII), the possibility cannot be overlooked. Therefore, the exact role of Mechanism IV in ketone (XX) formation must be determined in another fashion. When pivaldehyde (XXIII) was subjected to the deuteriosulfuric acid conditions, methyl isopropyl ketone (XX) was formed. Nmr analysis indicated no alpha hydrogens in the ketone (XX) product, while mass spectral analysis (Table II, p 18) showed mainly the d_4 compound to be present. These results are consistent with formation of methyl isopropyl ketone (XX) from pivaldehyde via steps (XXIII) $\longrightarrow$ (XXII) $\longrightarrow$ (XVIII) $\longrightarrow$ (XIX) $\longrightarrow$ (XX) (Mechanism IV). The resistance of intermediate ion (XVIII) towards proton exchange was demonstrated previously (p 20) when the intermediacy of allylic alcohols (XV) and (XVII) was considered. The pivaldehyde results support this demonstration and require proton exchange to occur prior to formation of protonated pivaldehyde (XXII) in Mechanism IV, if indeed such a scheme is to be used to account for the extensive exchange which is observed.

In envisioning a pathway which could account for the extensive proton exchange which is observed, the possible intervention of protonated cyclopropanes (p 4) was considered. The literature contains very little documentation of proton exchange in cyclopropanes. Thus, Baird and Aboderin[6] reacted cyclopropane itself with deuteriosulfuric acid to obtain an n-propanol fraction containing one deuterium atom per molecule, distributed among the three carbon atoms. This result might indicate that proton exchange in cyclopropanes does not occur. However, such exchange is not ruled out in our system and, therefore, such routes were considered. The two systems which can be formed from 2,2-dimethyl-1,3-propanediol (X) are indicated on p 25. Depuy and coworkers[19] have shown that cyclopropanols in acid media tend to ring open at the 1,2-and 1,3-bonds to give carbonyl compounds. When 2,2-dimethylcyclopropanol (XXIV) was subjected to the deuteriosulfuric acid reaction conditions (p 16), a mixture of pivaldehyde (XXIIIb), 3-methylbutyraldehyde (XXVI), and methyl isopropyl ketone (XXb and XXc) was formed. The pathway consistent with these results is shown on p 26. Methyl isopropyl ketone (XXb and XXc) was the major component of the mixture (80% by gas chromatography). Nmr analysis revealed the absence of alpha hydrogen. and the presence of considerable isopropyl hydrogen (sharp triplet, J = 2 cps). This observation suggests a non-extensive deuteration of the ketone (XX). Since 3-methylbutyraldehyde (XXVI) is

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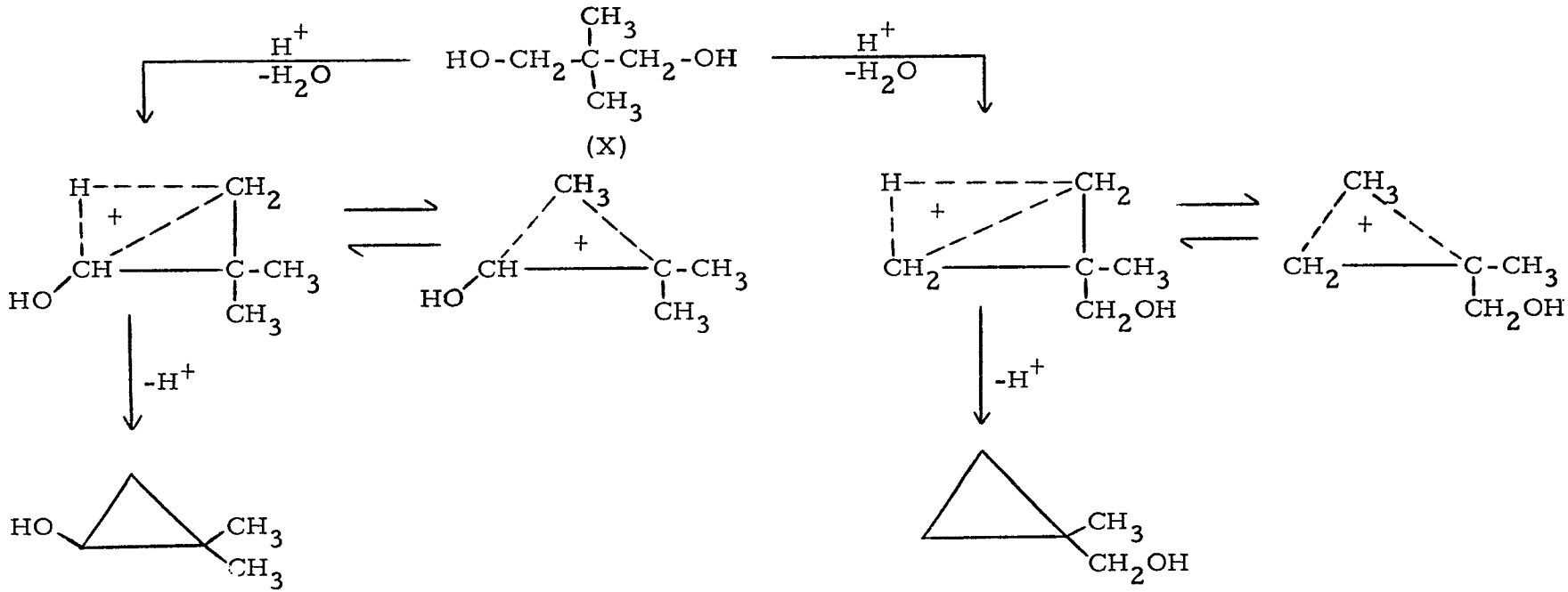
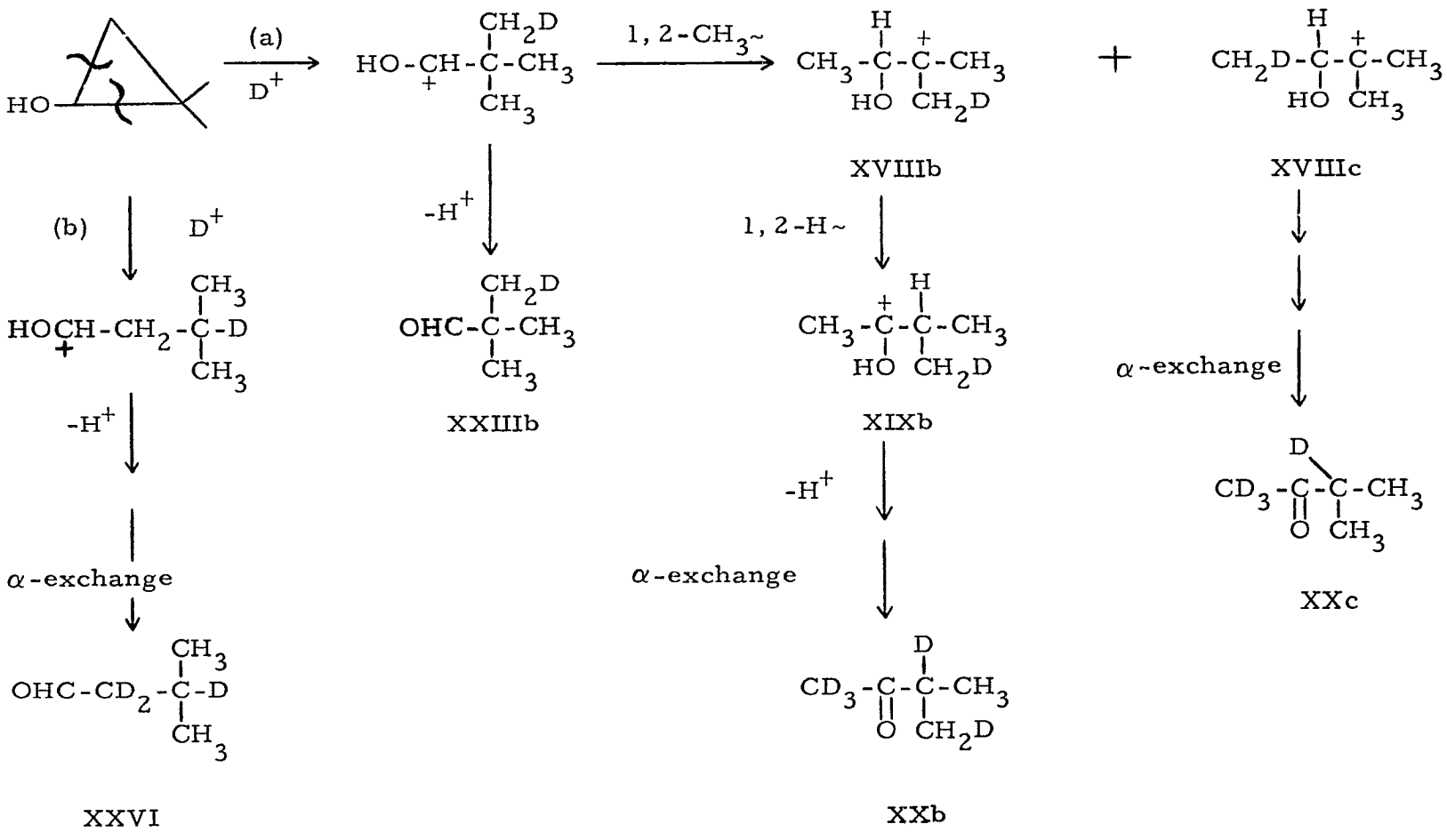
(19) C. H. DePuy and F. W. Breitbeil, J. Amer. Chem. Soc., 85, 2176 (1963).



(X)

XXIV

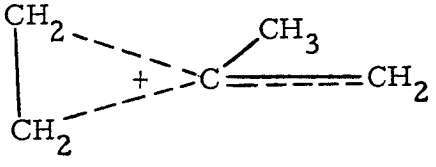
XXV



not found among the reaction products from 2,2-dimethyl-1,3-propanediol (X), and since the ketone (XX) from the diol is extensively deuterated to a large extent (Table II, p 18), 2,2-dimethylcyclopropanol (XXIV) can be ruled out as the major intermediate leading to extensive deuteration.

When 1-methylcyclopropylcarbinol (XXV) was subjected to the deuteriosulfuric acid reaction conditions (p 16) a 40% yield of a mixture consisting of methyl isopropyl ketone (XX) (90%), 2-methylbutyraldehyde (XIV) (10%), and a trace of pivaldehyde (XXIII) was obtained. The isotopic distribution of the ketone (XX) fraction (Table II, p 18) indicated very extensive deuteration. The ratio of the major products was very similar to that obtained from 2-methyl-2-buten-1-ol (XV) and 3-methyl-3-buten-2-ol (XVII) (p 20).

The 1-methylcyclopropylcarbinyl system has been studied in some detail. Thus, Roberts and coworkers[20] have proposed the intermediacy of a non-classical ion to account for the enhanced reactivity of this system. The intermediate ion is currently believed to possess structure (XXVII).[21]



XXVII

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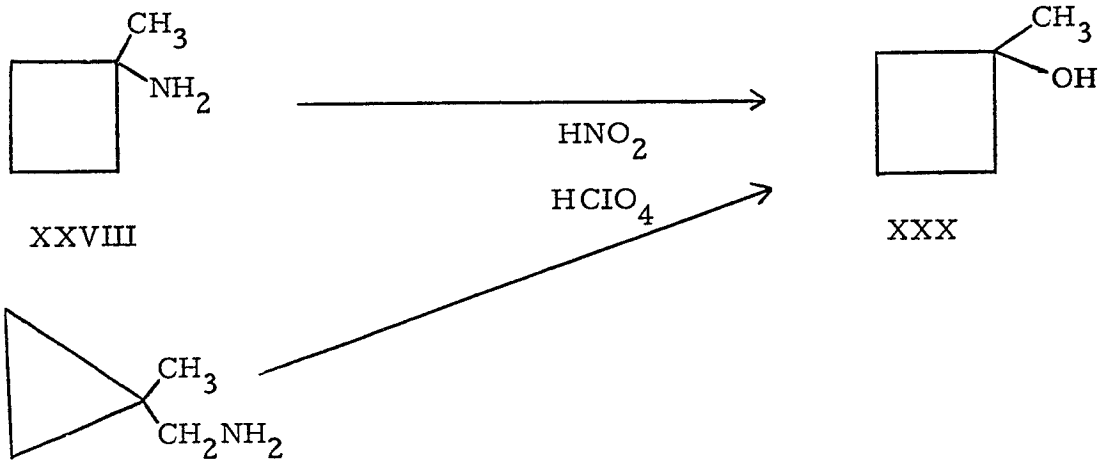
(20) E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, J. Amer. Chem. Soc., 83, 2719 (1961).

(21) H. G. Richey, Jr. and J. M. Richey, ibid., 88, 4971 (1966).

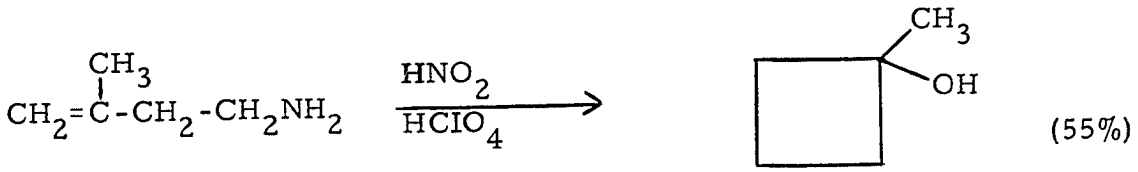
It has been observed that 1-methylcyclobutylamine (XXVIII) and 1-methylcyclopropylcarbinylamine (XXIX) upon reaction with nitrous acid in aqueous perchloric acid give 1-methylcyclobutanol (XXX) exclusively.[20]



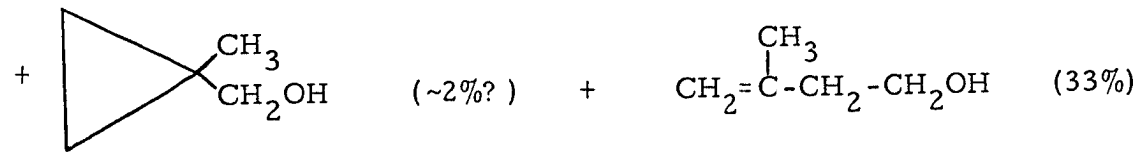
XXVIII XXX

XXIX

Deamination of 3-methyl-3-butenylamine (XXXI) in aqueous perchloric acid gave a complex mixture of alcohols identified as 55% 1-methylcyclobutanol (XXX), 33% 3-methyl-3-buten-1-ol (XXXII), 2% (±2%) 1-methylcyclopropylcarbinol (XXV), 4% 3-methyl-3-buten-2-ol (XVII, and 6% 2-methyl-2-buten-1-ol (XV).[20] It was suggested that the open-chain unsaturated alcohols are probably derived from the 3-methyl-3-butenyl cation. This species can react with solvent to give unrearranged alcohol, or to a smaller extent undergo a 1,2-hydride shift to form the resonance stabilized 1,2-dimethylallyl carbonium ion (XXXIII).

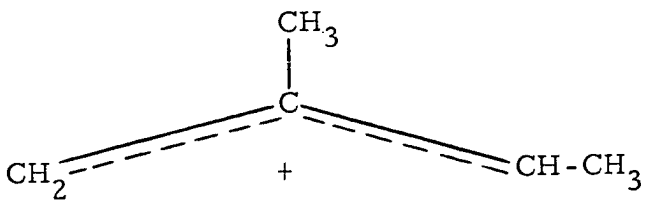


XXXI XXX (55%)



XXV (~2%?) + XXXII (33%)

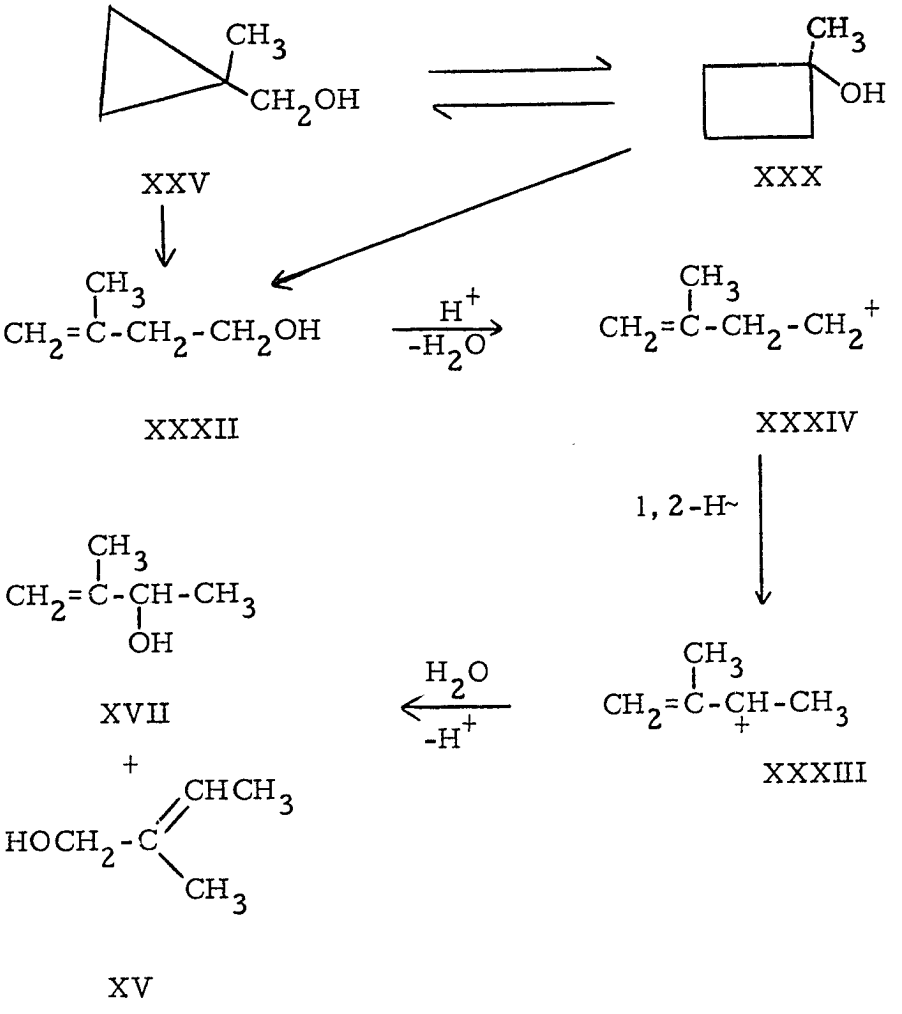
XVII (4%) + XV (6%)



XXXIII

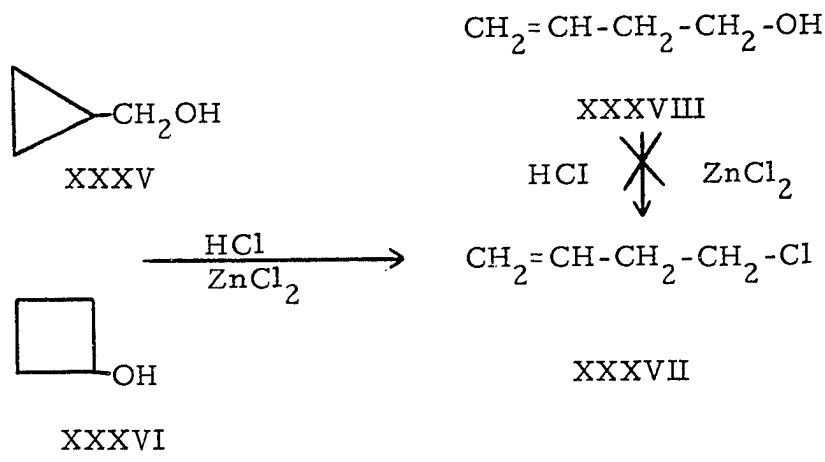
Reaction of (XXXIII) with water is expected to give both 2-methyl-2-buten-1-ol (XV) and 3-methyl-3-buten-2-ol (XVII). Since allylic alcohols (XV) and (XVII) have been shown to give methyl isopropyl ketone (XX) under the sulfuric acid reaction conditions (p 20), it is indeed possible that they are the source of methyl isopropyl ketone (XX) from 1-methylcyclopropylcarbinol (XXV), and arise by way of a similar mechanism (see Mechanism V).

MECHANISM V



It is therefore desirable to consider this pathway in more detail. 1-Methylcyclobutanol (XXX), under the deuteriosulfuric acid reaction conditions, afforded a 30% yield of a mixture of methyl isopropyl ketone (XX) (90%) and 2-methylbutyraldehyde (XIV) (10%). Time-of-flight mass spectrometry of the glc effluent of this mixture indicated that the ketone (XX) fraction was essentially <u>all</u> d_{10}. When 3-methyl-3-buten-1-ol (XXXII) was subjected to deuteriosulfuric acid reaction

conditions at normal concentrations of alcohol and acid, a 45% yield of higher molecular weight material was obtained. Only traces of methyl isopropyl ketone (XX) and 2-methylbutrayaldehyde (XIV) were obtained. Mass spectral analysis of the higher molecular weight material revealed a heavily deuterated system with a general formula $(C_5H_8)_n$. It has been observed that cyclopropylcarbinol (XXXV) and cyclobutanol (XXXVI) upon reaction with hydrochloric acid-zinc chloride readily afford allycarbinyl-chloride (XXXVII), while allylcarbinol (XXXVIII) reacts only under more strenuous conditions to give unidentified polymeric material.[22]



When 3-methyl-3-buten-1-ol (XXXII) was subjected to deuteriosulfuric acid reaction conditions at a 20-fold dilution of alcohol, a 20% yield of a mixture of methyl isopropyl ketone (XX) (90%) and 2-methylbutyraldehyde (XIV) (10%), and a 13% yield of high molecular weight material were obtained. A small amount of pivaldehyde (XXIII) was also present. The isotopic distribution of the ketone (XX) fraction (Table II, p 18)

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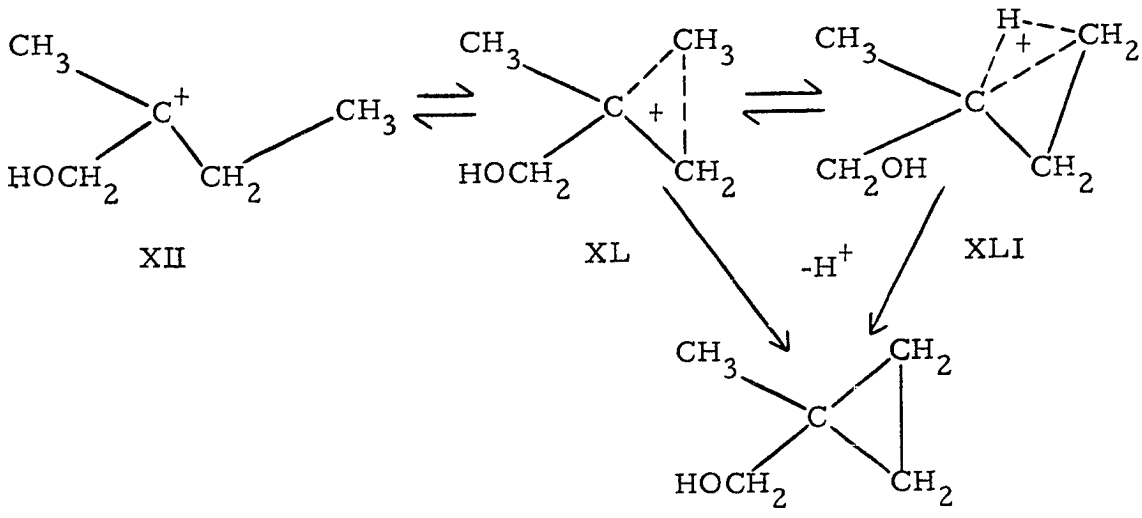
(22) J. D. Roberts and R. H. Mazur, ibid., 73, 2509 (1951).

indicated essentially complete deuteration. There was very little high molecular weight material formed from the reaction of either 1-methylcyclopropylcarbinol (XXV) or 1-methylcyclobutanol (XXX). In order for Mechanism V (p 30) to be consistent with these facts, the rate of formation of intermediate (XXXII) from either (XXV) or (XXX) must be slow relative to the rate of further reaction. This would be equivalent to having intermediate (XXXII) react at higher dilution, a condition which would be expected to greatly reduce bimolecular reactions which would lead to higher molecular weight products. Such has been shown to be the case. Thus, systems (XXV), (XXX), and (XXXII) have been shown to give a product very similar in composition to that obtainable from either 2-methyl-2-buten-1-ol (XV), or 3-methyl-3-buten-2-ol (XVII). In addition, the methyl isopropyl ketone (XX) fraction from each (under deuteriosulfuric acid conditions) is essentially all d_{10}, a condition which is necessary to completely explain the isotopic distribution of the ketone (XX) product from the reaction of 2,2-dimethyl-1,3-propanediol (X) (p 20). The results are thus consistent with the postulate that the methyl isopropyl ketone (XX) fraction from this reaction is generated from two separate pathways, one consisting of the allylic-shift mechanism (Mechanism III, p 19) and the other involving a 1-methylcyclopropylcarbinyl system (Mechanism V, p 30).

1-Methylcyclopropylcarbinol (XXV) can be pictured as arising at either or both of two points along Mechanism I, p 11. The direct product of dehydroxylation of 2,2-dimethyl-1-3-propanediol (X), i.e. structure (XI), might undergo cyclopropane formation as shown on p 25,

presumably through a protonated cyclopropane. Assuming the existence of structure (XI) (for, indeed, a methyl shift could be concerted with loss of water from protonated (X), giving structure (XII) directly),[15] there are several reasons why this is not likely to be the case. Firstly cyclopropane formation in neopentyl systems has been found to be unfavorable.[12] Secondly, 2-methylbutyraldehyde (XIV) gives, under the deuteriosulfuric acid reaction conditions, a methyl isopropyl ketone (XX) fraction with an isotopic distribution similar to that from 2, 2-dimethyl-1, 3-propanediol (X) (Table II, p 18), except for the d_5 species which is a good deal lower, and the d_6 and d_7 species which are correspondingly higher. Rapid α-exchange in the 2-methylbutyraldehyde (XIV) starting material would be expected to result in a smaller d_5 contribution to the ketone (XX) fraction from this source. A ketone (XX) fraction with an isotopic distribution similar to that obtained from diol (X) is also observed from 2-methyl-1, 2-butanediol (XXXIX) (Table II). This situation would require the reversibility of step (XI) $\longrightarrow$ (XII), which amounts to going from a tertiary to a primary carbonium ion. Furthermore, recovered starting material from the reaction of 2, 2-dimethyl-1, 1, 3, 3-tetradeuterio-1, 3-propanediol (Xa) is unchanged by nmr analysis. A reversible step (XI) $\longrightarrow$ (XII) would suggest hydrogen incorporation into the starting material, since steps (XII) $\longrightarrow$ (XIII) $\longrightarrow$ (XIV) have been shown to be reversible (p 16).

The remaining possibility involves formation of a cyclopropane from structure (XII), again presumably through a protonated cyclopropane intermediate. Structure (XL) can be viewed as a methyl-bridged ion

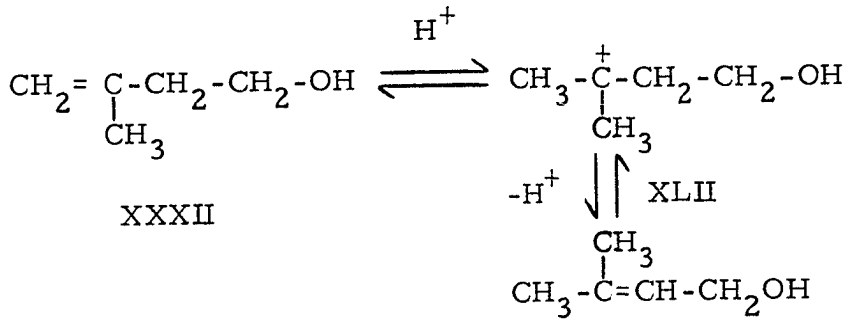


XII XL XLI XXV

which can equilibrate with edge-protonated species (XLI) to be followed eventually by proton loss to give 1-methylcyclopropylcarbinol (XXV).

The question remains as to the exact mode of extensive deuterium incorporation into the methyl isopropyl ketone (XX) fraction from the deuteriosulfuric acid reactions of 1-methylcyclopropylcarbinol (XXV), 1-methylcyclobutanol (XXX), and 3-methyl-3-buten-1-ol (XXXII). When 1-methylcyclopropylcarbinol (XXV) was subjected to the deuteriosulfuric acid reaction conditions, recovered starting material showed no deuterium by mass spectral analysis. During this reaction, 1-methylcyclobutanol (XXX) was obtained as a product. Mass spectral analysis revealed that it was also unlabeled. Both compounds (XXV and XXX) are stable under GLC conditions, and, therefore, thermal rearrangement is excluded. Extensive exchange by means of protonated cyclopropanes (p 4), or exchange through reversible formation of Roberts' "bicyclobutonium" ion (p 27) is thus ruled out. It has been shown (p) that neither 2-methyl-2-buten-1-ol (XV) nor 3-methyl-3-buten-2-ol (XVII) undergo extensive deuteration. This means that exchange must take place at some point

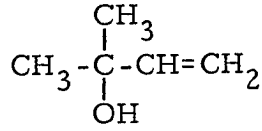
between species (XXXII) and (XXXIII) of Mechanism V (p 30). Let us consider exchange in 3-methyl-3-buten-1-ol (XXXII) itself. A reversible protonation of the double bond in this case would not be analogous to that considered in Mechanism I, p 11 (step (XVII)⟶(XVIII)). It was found (p 20) that deprotonation to reform 3-methyl-3-buten-2-ol (XVII) is evidently slower than a hydride shift to form a protonated ketone (XIX). In 3-methyl-3-buten-1-ol (XXXII), however, protonation of the double bond gives a positive charge one carbon removed from such a situation.



XXXII XLII XLIII

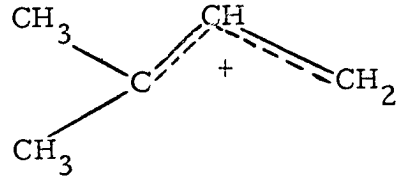
Deprotonation of (XLII) should give, in addition to (XXXII), 3-methyl-2-buten-1-ol (XLIII). 3-Methyl-2-buten-1-ol (XLIII), under sulfuric acid reaction conditions at normal concentrations, gives a 50% yield of high molecular weight material, which mass spectral analysis indicates is composed of (C_5H_8) units. At a 10-fold dilution of the alcohol the yield of high molecular weight material drops to 30% and an 8% yield of a mixture consisting of methyl isopropyl ketone (XX) (90%) and 2-methylbutyraldehyde (XIV)(10%) is obtained. This result is similar to that obtained from 3-methyl-3-buten-1-ol (XXXII) under deuteriosulfic acid reaction conditions (p 31). The allylic isomer of (XLIII),

2-methyl-3-buten-2-ol (XLIV), exhibits similar behavior under sulfuric acid reaction conditions. Allylic alcohols (XLIII) and (XLIV) would



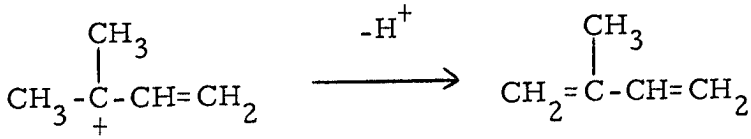
XLIV

be equilibrated under the sulfuric acid conditions by means of allylic carbonium ion (XLV). Depending on the concentration, this carbonium



XLV

ion can attack available olefins (at higher concentrations) or, at lower concentrations, form 3-methyl-3-buten-1-ol (XXXII) (steps (XLV) $\longrightarrow$ (XLIII) $\longrightarrow$ (XLII) $\longrightarrow$ (XXXII)) or form isoprene (XLVI). It has been reported[23] that the reaction of isoprene in 0.9% sulfuric



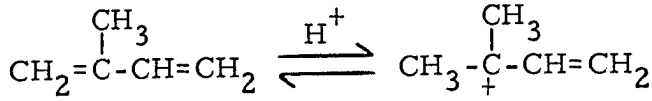
XLV XLVI

(23) T. Lennartz, Chem. Ber., 76B, 831 (1943).

acid-acetic acid, in the presence of inhibitors, gives a 25% yield of 3-methyl-2-buten-1-ol (XLIII), and a 75% yield of monoterpenes, sesquiterpenes, and diterpenes. Indeed, under the deuteriosulfuric acid reaction conditions, isoprene (XLVI) gave a small amount of a mixture of extensively labeled methyl isopropyl ketone (XX) (90%) and 2-methylbutyraldehyde (XIV)(10%), as indicated by nmr analysis, in addition to high molecular weight material. This result can be interpreted in terms of a 1,4-addition of water to isoprene (XLVI) to give 3-methyl-2-buten-1-ol (XLIII) which has been shown to yield methyl isopropyl ketone (XX) and 2-methylbutyraldehyde (XIV) in the ratio 9:1 (p 35). A 1,4-addition in the reverse sense would give 2-methyl-2-buten-1-ol (XV), which is directly involved in the formation of methyl isopropyl ketone (XX) by means of the allylic shift pathway (Mechanism I, p 11). Formation of (XV) from isoprene would involve an incipient secondary-allylic carbonium ion, as opposed to a tertiary-allylic carbonium ion in the formation of (XLIII). Even so, the failure to observe (XV) in the aforementioned report[23] does not exclude the possibility of its formation under more strenuous conditions.

All attempts at demonstrating exchange in isoprene (XLVI) itself proved fruitless. Thus, when isoprene (XLVI) was subjected to the deuteriosulfuric acid reaction conditions, in a manner analogous to that described for the reaction of 2-methylbutyraldehyde (XIV)(p 105), the isoprene (XLVI) which was swept over was found to be totally devoid of deuterium, as indicated by nmr analysis. Similarly, when isoprene (XLVI) was refluxed for up to 15 min in 45% deuteriosulfuric acid, no

deuterium incorporation into the recovered isoprene (XLVI) was observed. When refluxing was allowed to proceed beyond 15 min the isoprene (XLVI) was rapidly converted to heavily deuterated high molecular weight material. It was felt that protonation of isoprene would preferentially give (XLV), which is a tertiary-allylic carbonium ion. Reversibility of step (XLVI) ⟶ (XLV) would give a methyl exchanged ion (XLV) which could reform isoprene (XLVI) and undergo a



XLVI XLV

1,4-addition of water (p 40) to eventually form an extensively deuterated methyl isopropyl ketone (XX). The ion (XLV) could also combine with water to give 2-methyl-3-buten-2-ol (XLIV) which has been shown to give methyl isopropyl ketone (XX) (p 36). Because of an inability to demonstrate exchange in isoprene (XLVI), however, the exact role of this diene could not be determined and attention was returned to 3-methyl-3-buten-1-ol (XXXII).

Trenke and coworkers[24] have investigated the sulfuric acid catalyzed dehydration of 3-methyl-1,3-butanediol (XLVII). Under 5% sulfuric acid conditions at 102°C, the reported products are 3-methyl-3-buten-1-ol (XXXII), 3-methyl-2-buten-1-ol (XLIII), and

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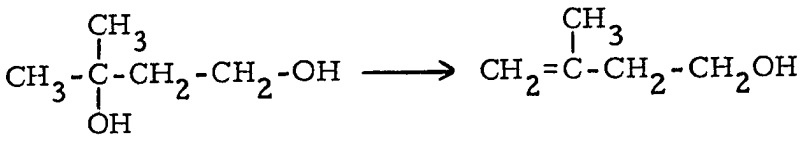
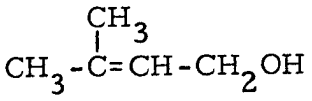
(24) K. M. Trenke, M. S. Nemtsov, and M. M. Kiseleva, Zh. Org. Khim., 3, 1327 (1967).



XLVII

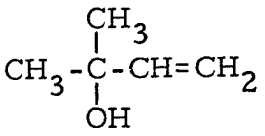
XXXII

+



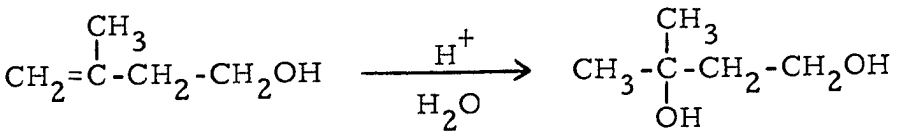
XLIII

+



XLIV

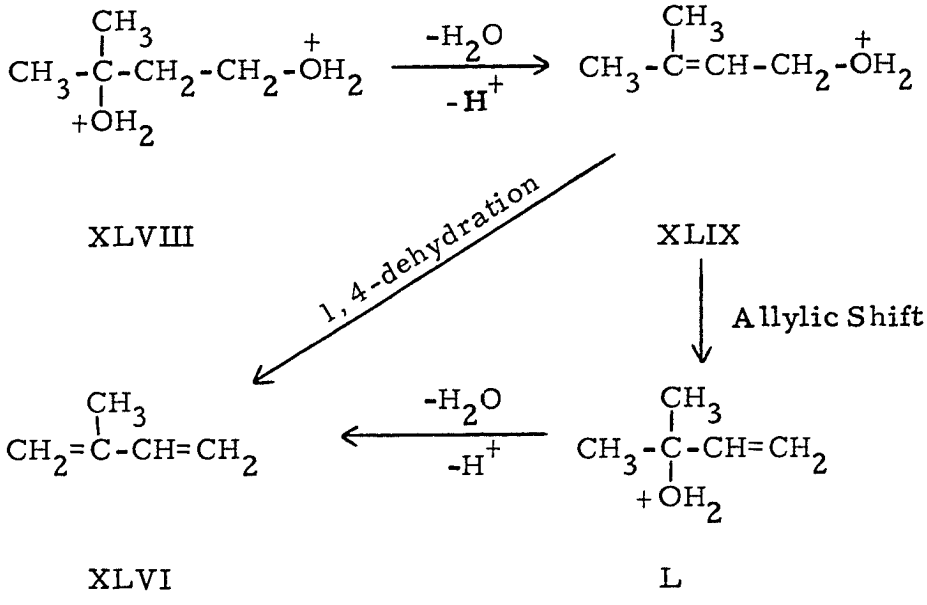
2-methyl-3-buten-2-ol (XLIV). A small amount of isoprene (XLVI) was also observed, which increased when the sulfuric acid concentration was increased to 10%. Reference was made to the ease of conversion of 3-methyl-3-buten-1-ol (XXXII) to 3-methyl-1, 3-butanediol (XLVII). Indeed, when 3-methyl-3-buten-1-ol (XXXII) was subjected to the above



XXXII XLVII

5% sulfuric acid conditions for 5 min, a 50% yield of 3-methyl-1, 3-butanediol (XLVII) was obtained. These results indicate a preference for reaction at the site of the double bond in (XXXII), at least under dilute acid conditions. The acid catalyzed dehydration of (XLVII) would be expected to involve the tertiary hydroxyl group, as this would lead to the

more stable (tertiary) carbonium ion. Under more acidic conditions, simultaneous involvement of both hydroxyl groups may occur, through a dipositive species (XLVIII). Stepwise dehydration (XLVIII)⟶(XLIX)⟶(L)⟶(XLVI), including 1,4-dehydration (XLIX)⟶(XLVI), would give isoprene (XLVI).

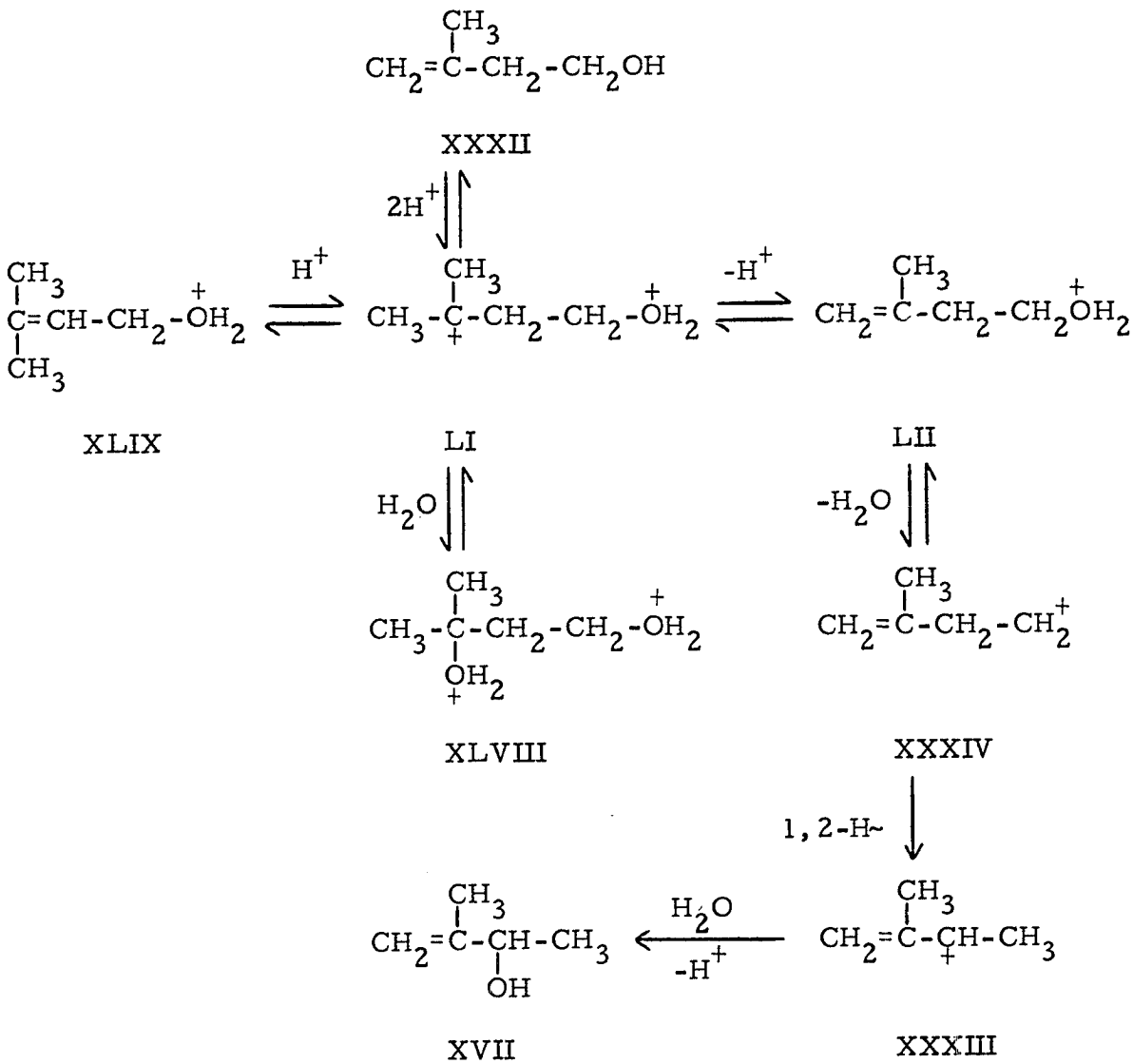


XLVIII XLIX

XLVI L

When 3-methyl-3-buten-1-ol (XXXII) was subjected to the 50% sulfuric acid reaction conditions (p 31), very little starting material was swept over. This could be an indication of participation by the diprotonated diol (XLVIII) and/or its carbonium ion equivalent (LI), as shown in Mechanism VI. According to that scheme, all systems leading to 3-methyl-3-buten-2-ol (XVII), which has been shown to yield the desired products (p 20), are charged and, therefore, non steam-distillable. The ease of interconversion of systems (XLVII) and (XXXII) suggests that the above may provide a means of explaining the extensive deuteration in the ketone (XX) product when deuteriosulfuric acid

MECHANISM VI



is employed as a medium for the acid catalyzed rearrangement of 2,2-dimethyl-1,3-propanediol (X). Since in acid media an equilibrium probably exists among systems (LII), (LI), and (XLIX), the isolated 3-methyl-1,3-butanediol (XLVII) from the deuteriosulfuric acid reaction of 3-methyl-3-buten-1-ol (XXXII) should exhibit deuterium incorporation. Various reaction conditions were employed in an

attempt to demonstrate this phenomenon. At temperatures above 75° C 3-methyl-3-buten-1-ol (XXXII) solutions (3-5%) in 37 and 45% deuteriosulfuric acid gave 90% of high molecular weight material, nmr analysis of which revealed extensive deuteration. This result is similar to that obtained under normal reaction conditions (p 31). At 5% deuteriosulfuric acid (102° C), a 65% yield of 3-methyl-1,3-butanediol (XLVII) was obtained. Nmr and mass spectral analysis showed little deuterium incorporation. At 10% deuteriosulfuric acid (118° C), a 5% yield of diol (XLVII), and a considerable amount of high molecular weight material were obtained. The nmr spectrum of the diol (XLVII) fraction showed considerable deuterium content, mainly in the methyl groups (p 116). The mass spectrum was compared with that of unlabeled diol (XLVII). 3-Methyl-1,3-butanediol (XLVII) shows no molecular ion; m/e 89 $(M-CH_3)^+$ is shifted mainly to m/e 93 and 94 in the product from deuteriosulfuric acid; m/e 71 $(M-CH_3+H_2O)^+$ is shifted mainly to m/e 74, 75, and 76; m/e 59 $(CH_3-\overset{OH}{\underset{CH_3}{C}}+)$ is shifted mainly to m/e 64, 65 and 66; m/e 43 (CH_3CO^+) is shifted to m/e 45 and 46. These results show quite conclusively that proton exchange does occur on formation of 3-methyl-1,3-butanediol (XLVII) from 3-methyl-3-buten-1-ol (XXXII) (mainly involving the methyl groups, p 116), presumably by way of a reversible step (LII)⟶(LI). As a result, any methyl isopropyl ketone (XX) formed by a series of steps involving either of these intermediates would be deuterated. Indeed, under 45% deuteriosulfuric acid reaction conditions, at high dilution, an extensively deuterated methyl isopropyl ketone (XX) product is obtained from 3-methyl-3-buten-1-ol

(p 31). The higher acid concentration and higher temperature employed might be expected to encourage even greater exchange, through reversible step (LII)⟶(LI), than is observed above for the case of 10% deuteriosulfuric acid at 118°C. Unfortunately, diol (XLVII) is very reactive, and attempts at isolation under more strenuous conditions met with failure in the form of high molecular weight material (p 42). Under the ordinary deuteriosulfuric acid reaction conditions 3-methyl-3-buten-1-ol gave, in effect, condensation products of isoprene only (p 31). These monoterpene, sesquiterpene, and diterpene systems are, however, heavily deuterated, and the possibility exists that exchange may occur on the monomeric units through intervention of 3-methyl-1,3-butanediol (XLVII), whose diprotonated form (XLVIII) could undergo mono-dehydration to (LII) and (XLIX) (Mechanism VI) or di-dehydration to isoprene (XLVI). 3-Methyl-2-buten-1-ol (XLIII) and isoprene (XLVI) have been mentioned previously in connection with the acid catalyzed formation of monoterpenes, sesquiterpenes, and diterpenes (p 36). In 50% sulfuric acid, both isoprene (XLVI) and 3-methyl-3-buten-1-ol (XXXII) give a 15% yield of methyl isopropyl ketone (XX) (90%) and 2-methylbutyraldehyde (XIV) (10%) plus a small amount of high molecular weight material. This is in sharp contrast with the behavior of these compounds under the 45% deuteriosulfuric acid reaction conditions, where high molecular weight products predominate (p 37). Noyce and coworkers[25] have recently investigated

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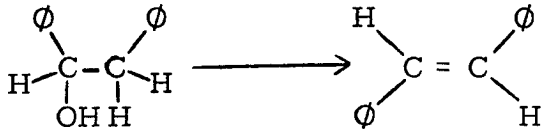
(25) D. S. Noyce, D. R. Hartter, and R. M. Pollack, J. Amer. Chem. Soc., 90, 3791 (1968).

the sulfuric acid catalyzed dehydration of 1,2-diphenyl ethanol to give trans-stilbene. They report that the rate of dehydration in 50%

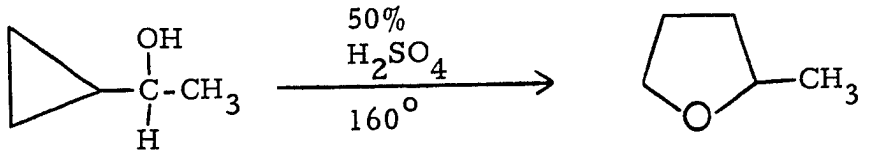


deuteriosulfuric acid is greater than that in 50% sulfuric acid by a factor of 1.62. This greater dehydrating ability of deuteriosulfuric acid (which may indicate that it is indeed a stronger acid) could account for the aforementioned observations. The intermediacy of 3-methyl-1,3-butanediol (XLVII) can be suggested for the cases of both 3-methyl-3-buten-1-ol (XXXII) and isoprene (XLVI) (p 37). Under the influence of deuteriosulfuric acid, the rate of dehydration of diol (XLVII) may become sufficiently great to encourage formation of systems which have been observed to give polymer under more concentrated conditions (p 35). However, reduction of acid concentration to a calculated 30% has little effect upon product composition, and, therefore, the situation does not seem to be one of acid strength.

An alternative explanation involves invoking a primary isotope effect during the exchange process. Monodehydration of 3-methyl-1,3-butanediol (XLVII) can proceed to give either 3-methyl-3-buten-1-ol (XXXII) or 3-methyl-2-buten-1-ol (XLIII) or its allylic isomer (XLIV) (p 35). When diol (XLVII) was subjected to glc treatment (20% DC550 on 60/80 chromosorb P, col length 8 ft., col temp. 140°, inlet temp. 190°, 60 cc of helium per min) (XXXII) was observed as the major decomposition product. Although the conditions are not the same, glc

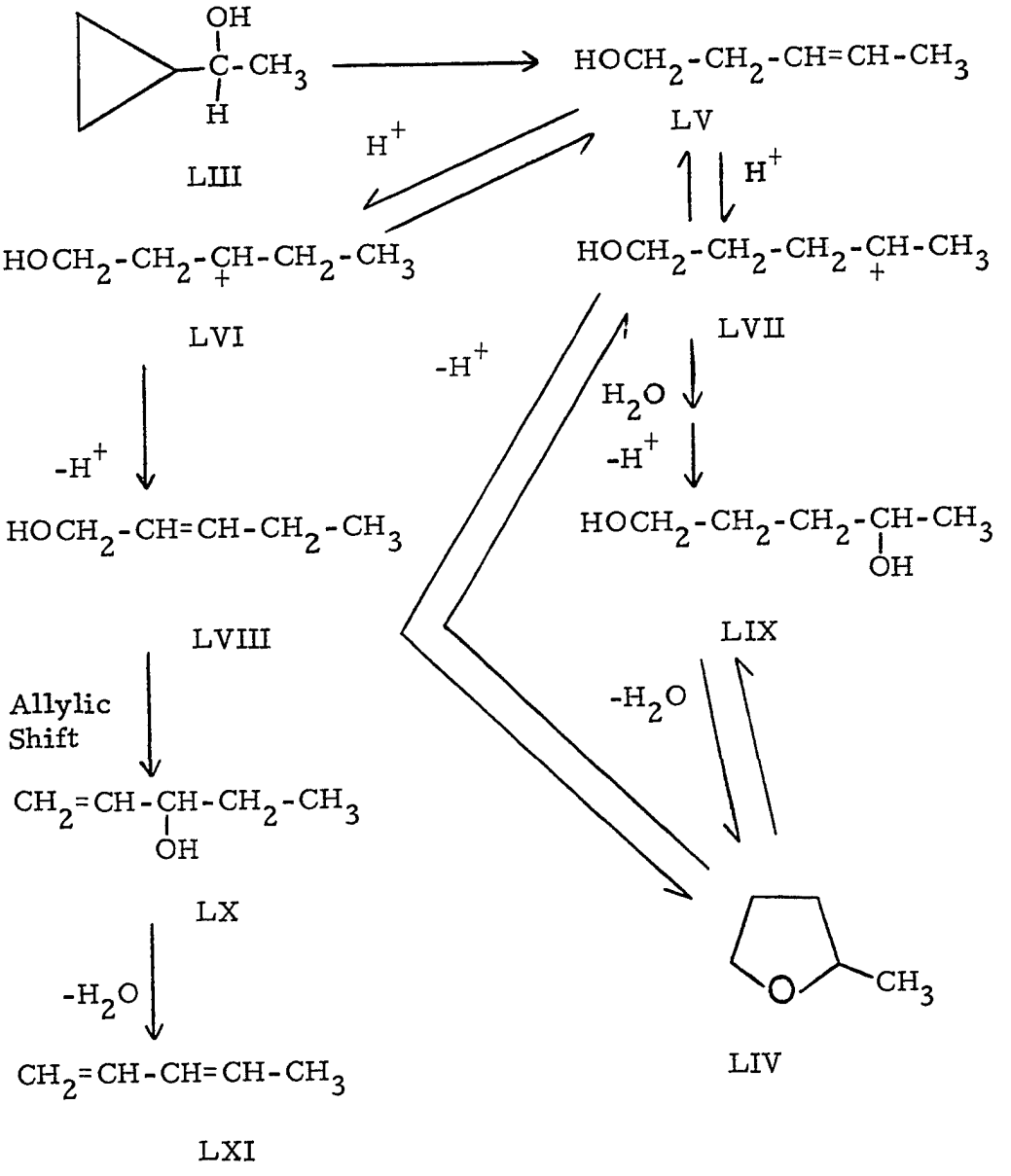
treatment did produce a kinetically favored product. Referring to Mechanism VI (p 41), if (LII) is a kinetic product of dehydration of (LI), then reversible step (LI)⟶(LII) may occur many times before any thermodynamically favored (XLIX) is formed. At concentrated conditions, system (XLIII) has been shown to give mainly polymer, even under ordinary sulfuric acid treatment. Thus, any effect which could shift the equilibrium appreciably towards (XLIX) might be expected to result in polymer formation. In deuteriosulfuric acid, a reversible step (LI)⟶(LII) would proceed to incorporate deuterium into the methyl groups. Eventually, system (LI) would have a choice of losing either deuterium to form (LII) or hydrogen to form (XLIX). A normal primary isotope effect of 4-5 might be sufficient to drive the equilibrium towards (XLIX). T. Lennartz[23] has reported that the sulfuric acid catalyzed reaction of isoprene (XLVI) produces more terpene when 3-methyl-2-buten-1-ol (XLIII), or its allylic isomer (XLIV) is added.

The reasonableness of proposing the intermediacy of 3-methyl-3-buten-1-ol (XXXII) in the rearrangement of 1-methylcyclopropylcarbinol (XXV) can be extended through consideration of another cyclopropylcarbinyl skeleton. When cyclopropyl methyl carbinol (LIII) was subjected to the 50% sulfuric acid reaction conditions, a 5% yield of 2-methyltetrahydrofuran (LIV) was obtained and a large amount of higher molecular weight material was produced. A reasonable pathway for formation of (LIV) is outlined as Mechanism VII. 3-Penten-1-ol (LV) is the analog of 3-methyl-3-buten-1-ol (XXXII), and can be protonated to give two essentially equally probable carbonium ions, (LVI) and



LIII LIV

MECHANISM VII



(LVII). Carbonium ion (LVI) can proceed to give 1,3-pentadiene (LXI) which, under acidic conditions, could polymerize to account for the large amount of higher molecular weight material that is observed. Carbonium ion (LVII) can either undergo ring closure to give 2-methyltetrahydrofuran (LIV) directly or react with water to give 1,4-pentanediol (LIX). The case for tetrahydrofuran formation from 1,4-diols has been well documented.[26,27] For example, it has been observed that the reaction of 1-methyl-1,4-cycloheptanediol (LXII) with 35% deuteriosulfuric acid gives 1-methyl-8-oxabicyclo 3.2.1 octane (LXIII) as the only steam distillable product (p 58).

The dehydration of unsubstituted cyclopropylcarbinol (LXIV) with hot 50% sulfuric acid has been reported to yield 1,3-butadiene (LXV) exclusively (see Mechanism VIII). Although two distinct carbonium ions (LXVII and LXVIII) can be pictured as arising from a 3-buten-1-ol (LXVI) intermediate, it is likely that only (LXVIII) is formed as protonation in the reverse sense would yield a primary carbonium ion (LXVII) which is an energetically unfavorable situation. The failure to observe tetrahydrofuran among the reaction products could be accounted for by invoking this instability of ion (LXVII). By analogy with the formation of methyl isopropyl ketone (XX) from 3-methyl-3-buten-1-ol (XXXII) (p 31), 3-penten-1-ol (LV)(p 46) and 3-buten-1-ol (LXVI)

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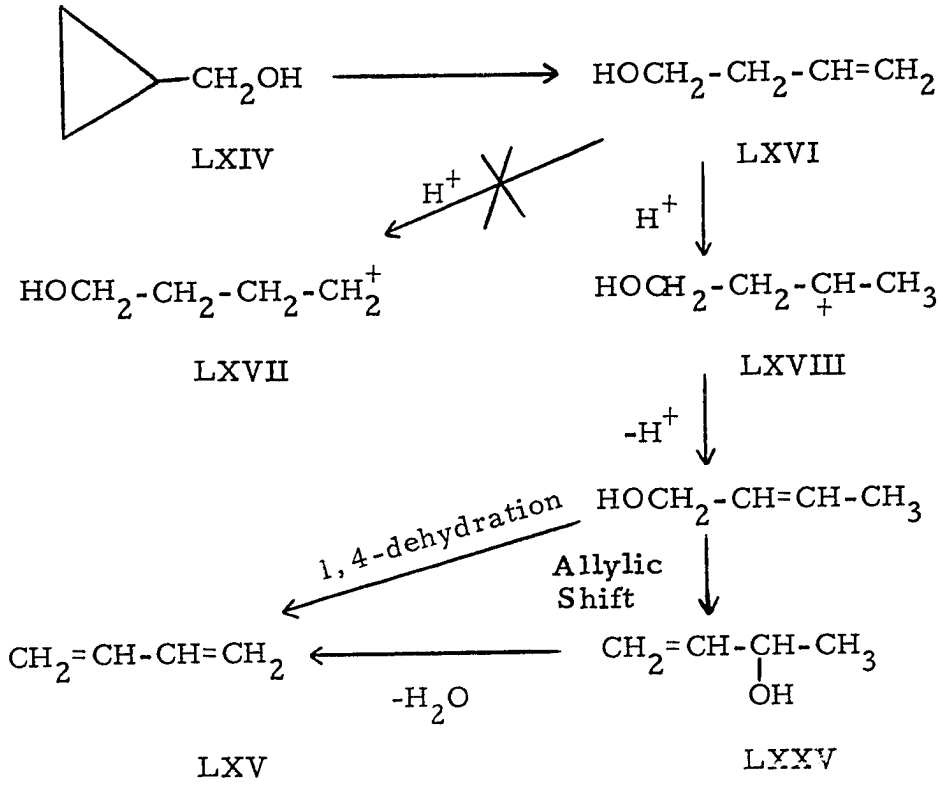
(26) B. T. Gillis and P. E. Beck, J. Org. Chem., 28, 1388 (1963).

(27) A. P. Krapcho and B. P. Mundy, J. Heterocycl. Chem., 2, 355(1965).

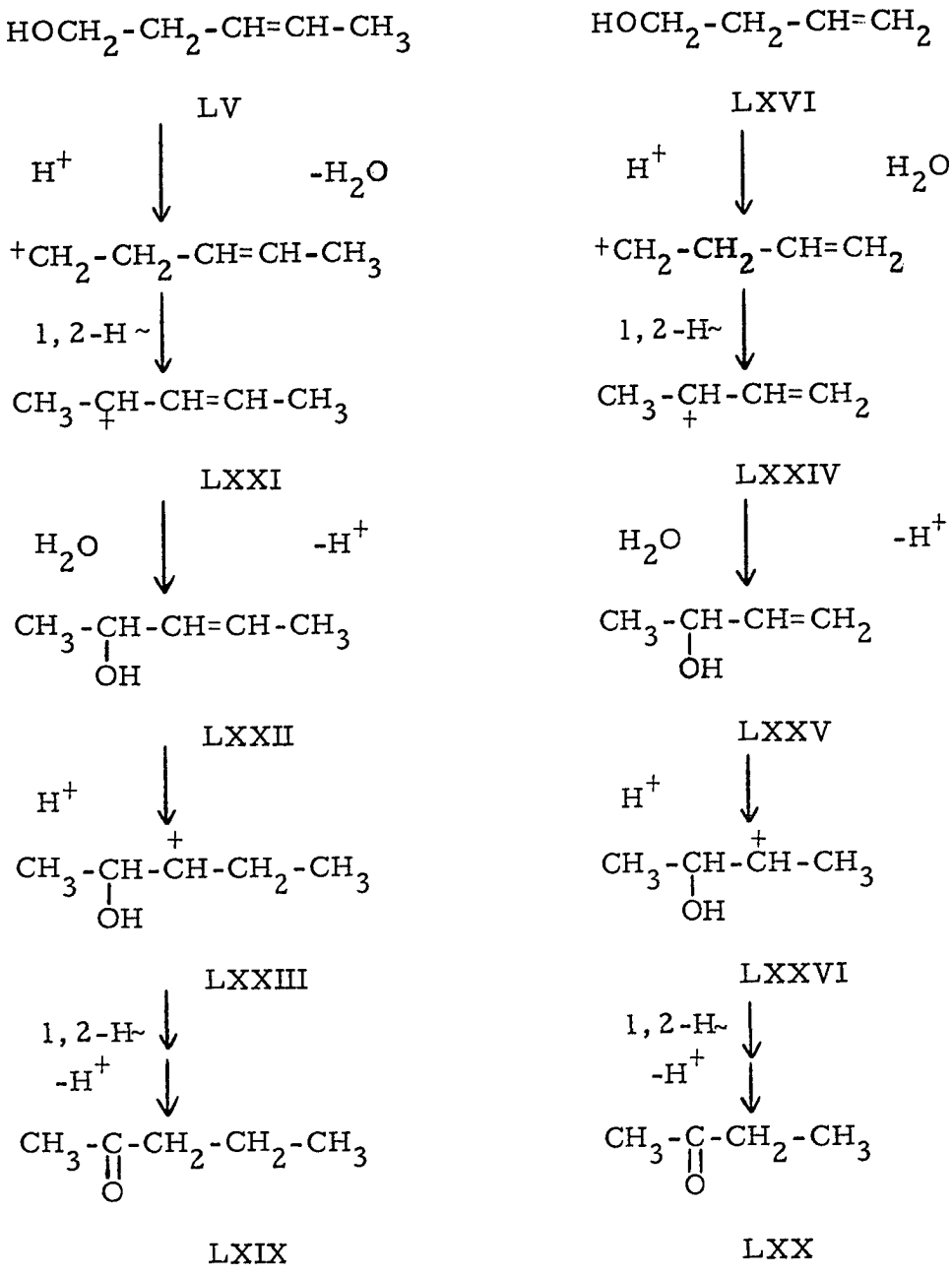
MECHANISM VIII



(p 49) would be expected to yield 2-pentanone (LXIX) and 2-butanone (LXX), respectively (Mechanism IX).

The fact that neither of these ketones (LXIX nor LXX) is found among the reaction products may be explained by considering the relative basicities of oxygen versus the double bond in the intermediates (LXXII), (LXXV), and (XVII). In order to obtain a ketone product, protonation must occur at the site of the double bond. Intermediates (LXXII) and (LXXV) give a secondary carbonium ion in this case, whereas intermediate (XVII) yields a tertiary carbonium ion. Since all three intermediates (LXXII, LXXV, and XVII) yield secondary allylic carbonium ions upon oxygen protonation (LXXI), (LXXIV), and

MECHANISM IX



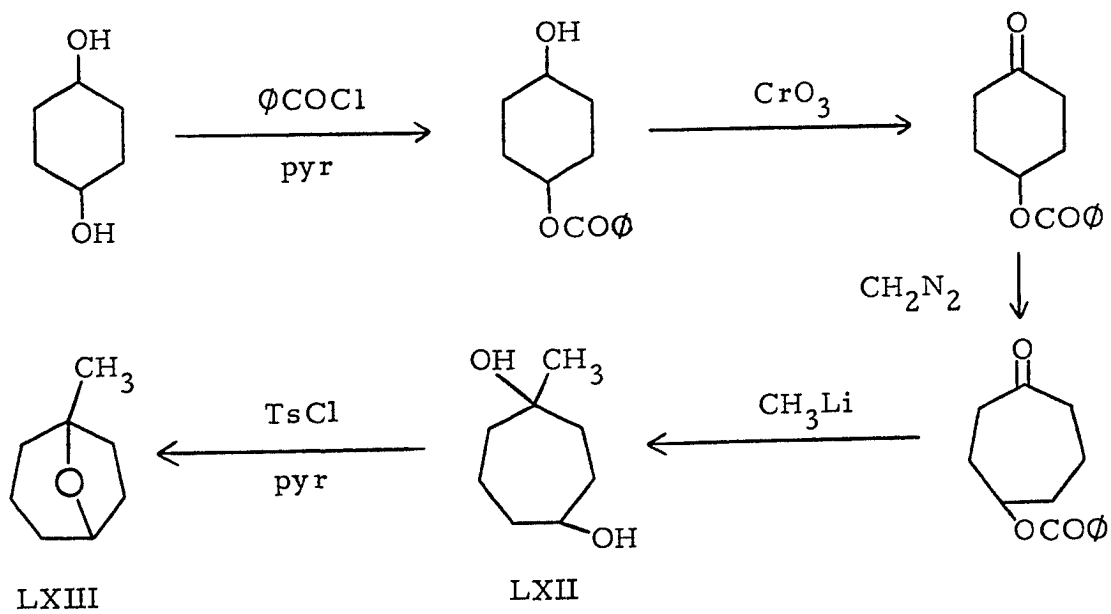
(XXXIII) (p 41) respectively, the observed difference in behavior among (XXV), (LIII), and (LXIV) may indeed be a reflection of the well-known difference in stability between a tertiary and a secondary carbonium ion.

Thus, the intervention of a cyclopropylcarbinyl to homoallyl isomerization (p 30) accounts nicely for the above observations. We conclude that such a pathway is involved in the rearrangement of 2,2-dimethyl-1,3-propanediol (X)(p 17). 1,3-Hydride shifts appear to be absent .

(B) The Rearrangement of 1,1-Bis-(hydroxymethyl)cyclohexane

Under the 50% sulfuric acid reaction conditions (p 13), 1,1-bis-(hydroxymethyl)cyclohexane (LXXVII) gives a 60% yield of five steam-distillable compounds which, in order of elution from the gas chromatograph, were identified as: 1-Methyl-8-oxabicyclo[3.2.1]octane (LXIII), α-methylcyclohexanecarboxaldehyde (LXXVIII), methyl cyclohexyl ketone (LXXIX) α-methylcycloheptanone (LXXX), and cycloheptanecarboxaldehyde (LXXXI). The ether (LXIII) was identified by comparison of its ir spectrum with that of an authentic sample, prepared according to Scheme I. The carbonyl compounds (LXXVIII), LXXIX, LXXX, and LXXXI) were identified by analysis of their nmr spectra and by their DNPH derivatives.

SCHEME I



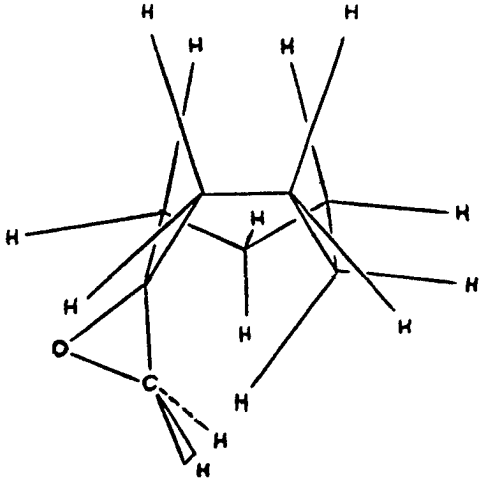
LXIII LXII

Under the reaction conditions, α-methylcyclohexanecarboxaldehyde (LXXVIII) was partially converted to methyl cyclohexyl ketone (LXXIX) and α-methylcycloheptanone (LXXX), while α-methylcycloheptanone (LXXX) was partially converted to methyl cyclohexyl ketone (LXXIX), and cycloheptanecarboxaldehyde (LXXXI) gave all of the observed products (LXIII, LXXVIII, LXXIX, LXXX, and LXXXI). Methyl cyclohexyl ketone (LXXIX) remained unchanged under the reaction conditions. The ether (LXIII) was not subjected to the reaction conditions directly. However, the fact that 1-methyl-1,4-cycloheptanediol (LXII), under 35% deuteriosulfuric acid reaction conditions, gave only (LXIII), serves as indirect evidence that (LXIII) is not converted to the other products (LXXVIII, LXXIX, LXXX, and LXXXI), at least at this acid concentration. The amount of methyl cyclohexyl ketone (LXXIX) obtained from 1,1-bis-(hydroxymethyl)cyclohexane (LXXVII) decreases with decreasing acid concentration until at 35% sulfuric acid (LXXIX) is a very minor component of the product mixture. If a common intermediate is involved in the reactions of diols (LXXVII) and (LXII), the absence of methyl cyclohexyl ketone (LXXIX) as a reaction product of 1-methyl-1,4-cycloheptanodiol (LXII) at 35% acid does not rule out its formation under the more strenuous 50% sulfuric acid conditions employed as a standard in this discussion.

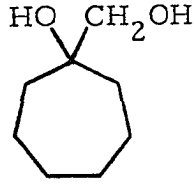
Under conditions of preparative gas chromatography (20% DC550 on 60/80 mesh Chromosorb P, 160°), the aldehyde products (LXXVIII and LXXXI) were partially converted to their respective carboxylic acids, and, therefore, mass spectral analysis was not attempted on these fractions.

(1) Results and Discussion of System I

Assuming a mechanism (Mechanism X) similar to that proposed for the reaction of 2, 2-dimethyl-1, 3-propanediol (p 11), the expected products from the 50% sulfuric acid catalyzed rearrangement of 1, 1-bis-hydroxydeuteriomethyl)cyclohexane (LXXVIIa) are shown (p 54). The nmr spectrum of the cycloheptanecarboxaldehyde (LXXXI) fraction shows appreciable aldehyde-hydrogen, suggesting that an exchange process analogous to that observed in the α -methylbutyraldehyde system is in operation (p 16). A ring expansion here is equivalent to a methyl migration in the 2, 2-dimethyl-1, 3-propanediol system (p 13). The formation of 1-methyl-8-oxabicyclo[3. 2. 1]octane (LXIII) can be most easily formulated in terms of a 1, 5-hydrogen transfer process, involving diol (LXXXII) and/or epoxide (LXXXIII).[28] Bearing in mind these



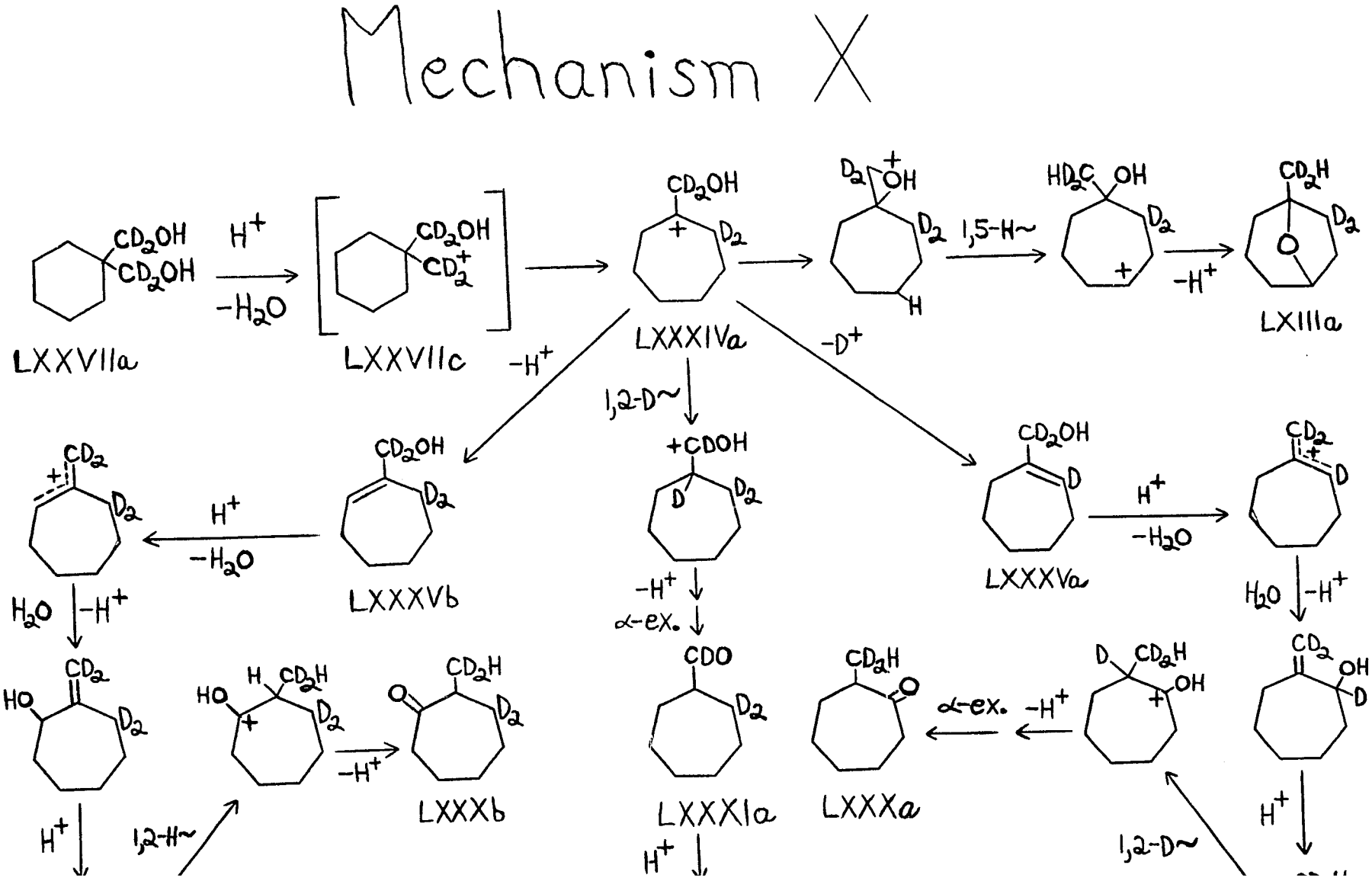
LXXXIII

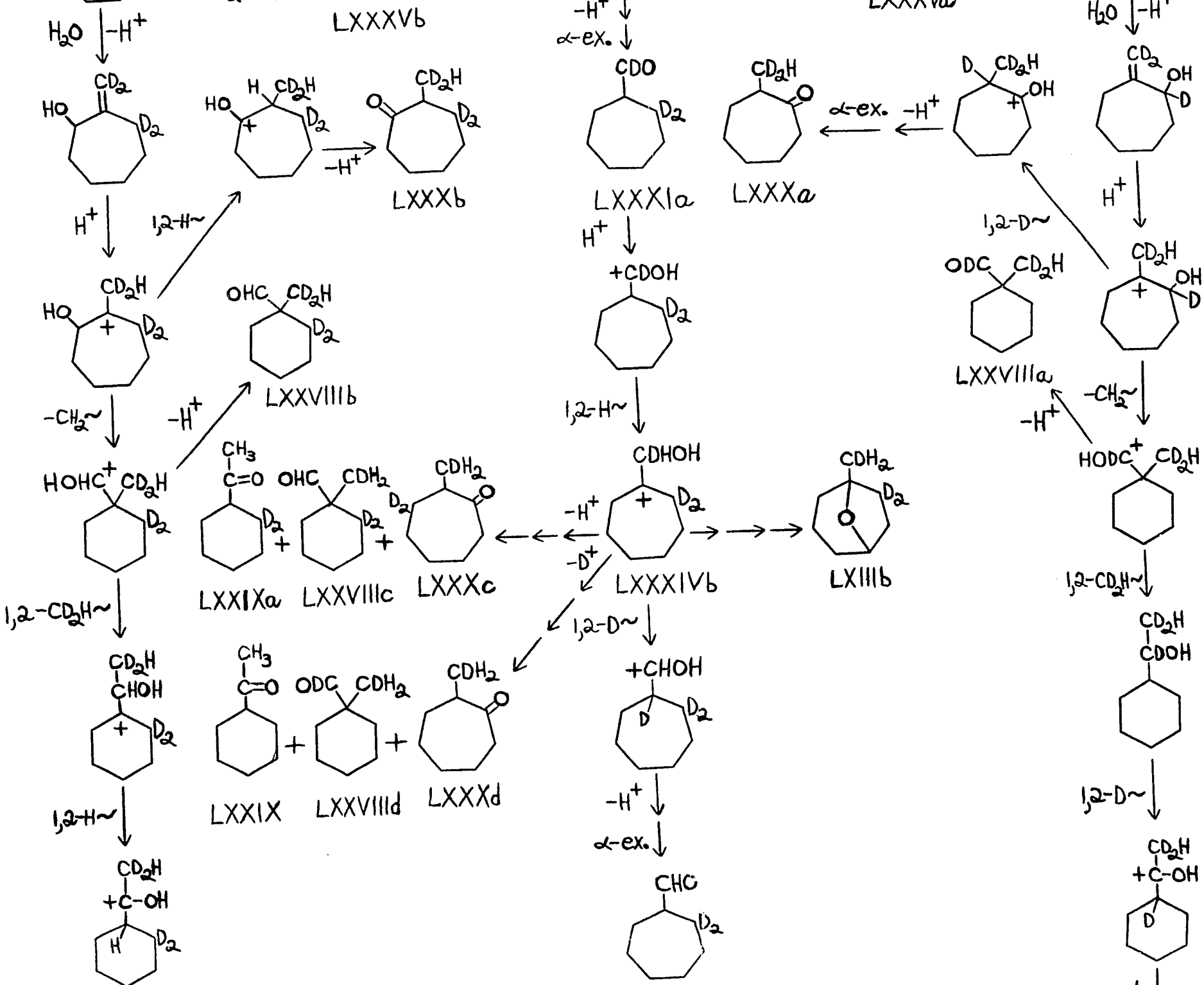


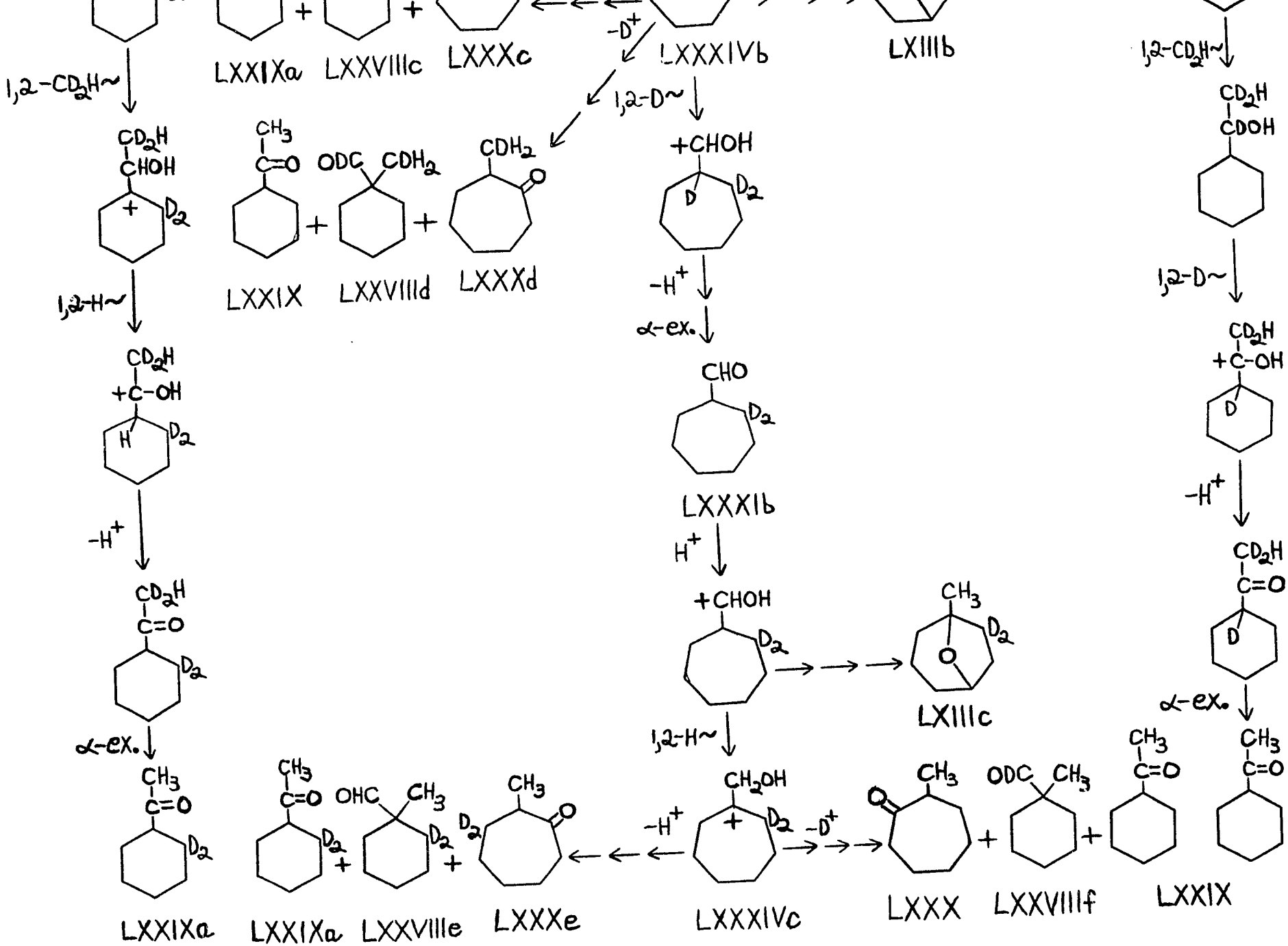
LXXXII

(28) L. H. Schwartz, M. Feil, A. J. Kascheres, K. Kaufmann, and A. M. Levine, Tetrahedron Letters, 39, 3785 (1967).

Mechanism X

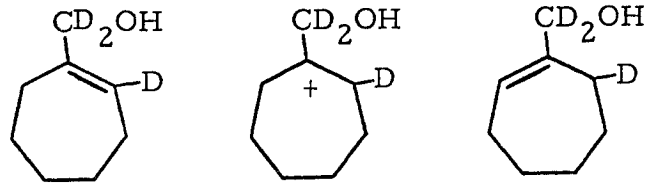






considerations, the bicyclic ether (LXIII) fraction would be expected to be composed of d_4, d_3, and d_2 species, the factor governing this distribution being the isotopic content of the ring expanded tertiary carbonium ion, that is, the relative amounts of (LXXXIVa), (LXXXIVb), and (LXXXIVc) (Mechanism X). The actual isotopic distribution, as indicated in Table III (p 56), shows that the major species, in fact, is that in which no deuterium is present. Exchange on carbonium ion (LXXXIVa) is ruled out on the basis of evidence to be presented (see p 58), and by analogy with the α-methylbutyraldehyde system, which has been shown not to undergo such exchange (p 16). The possibility of exchange occurring on the product (LXIII) itself will be discussed on p 58.

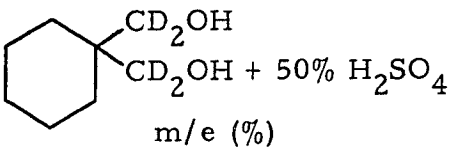
According to Mechanism X, the methyl cyclohexyl ketone (LXXIX) fraction should contain d_0 and d_2 species only. The actual results (Table III) seem to verify this prediction, where the 5% d_1 can be attributed to a slight contribution from the sequence of steps (LXXXVa) $\longrightarrow$ (LXXXIVd) $\longrightarrow$ (LXXXVc) (Step (LXXXVa) $\longrightarrow$ (LXXXIVd) is analogous to that observed in the 2-methyl-2-buten-1-ol (XV) system, which gave



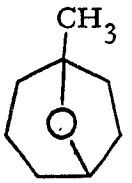
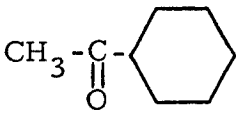
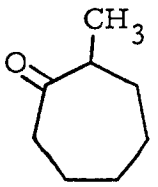
LXXXVa LXXXIVd LXXXVc

some α-methylbuturaldehyde (p. 20)), and the traces of d_3 and d_4 can be considered as representing deuterium alpha to a carbonyl in a

TABLE III [a]



m/e (%)

Product	126	127	128	129	130
	d_0	d_1	d_2	d_3	d_4
 LXIII	88.7	7.9	2.7	0.7	—
 LXXIX	42.1	5.1	49.9	1.7	1.2
 LXXX	18.4	9.2	35.6	16.4	20.4

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

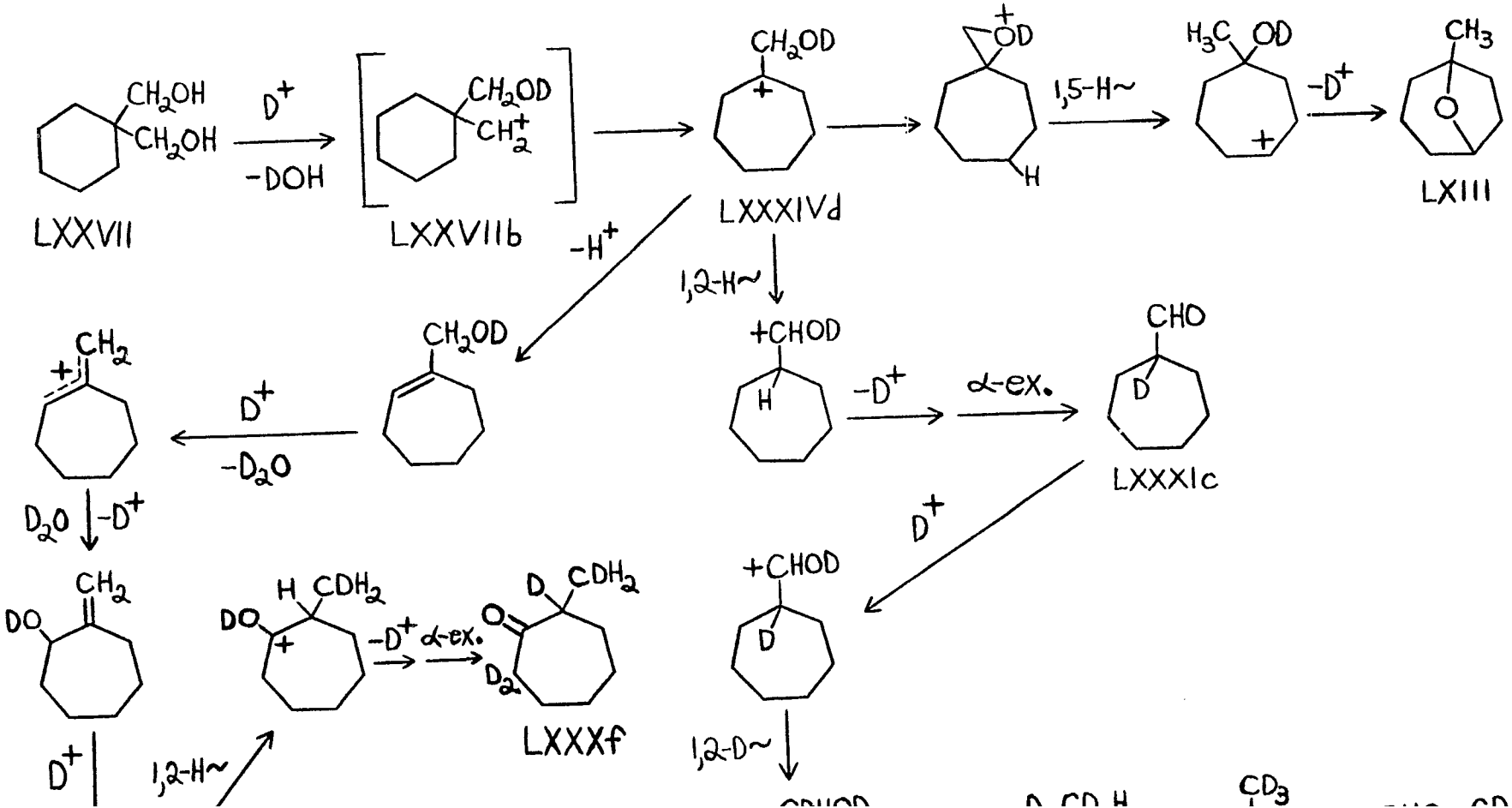
system which is not exhibiting complete alpha-exchange. Since alpha-exchange is an equilibrium process, complete exchange would not be expected and, indeed, this has been shown to be the case for methyl isopropyl ketone (see p 17). Although the above appears to provide a simple and complete explanation of the observed isotopic distribution, evidence obtained from another deuterium labeling approach (see p 66) complicates the picture appreciably.

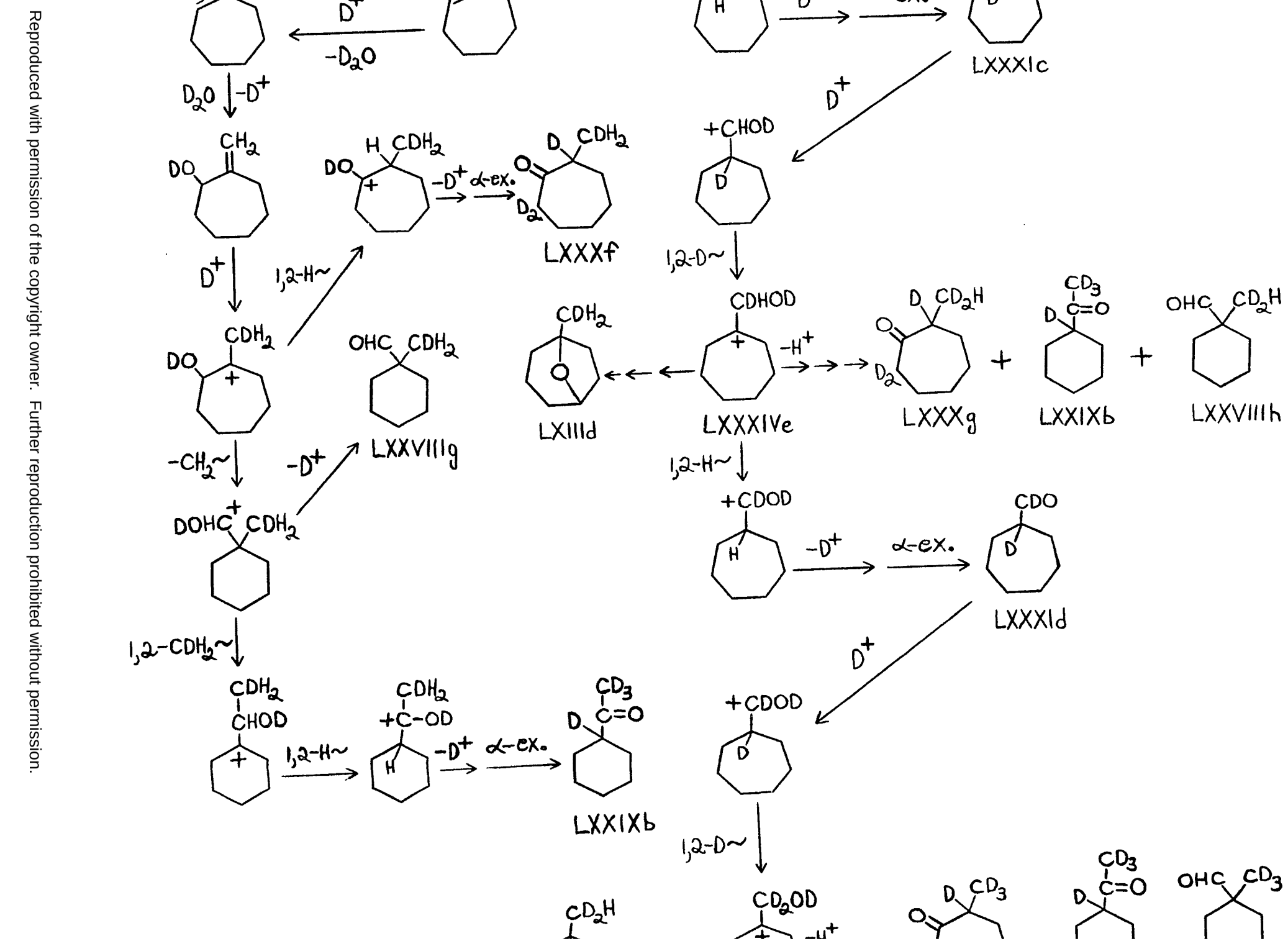
Mechanism X suggests that the α - methylcycloheptanone (LXXX) fraction should contain d_4, d_3, d_2, d_1, and d_0 species. Table III shows that appreciable amounts of all five species are present. The d_4 species can be pictured as arising from carbonium ion (LXXXIVa), while carbonium ion (LXXXIVb) would lead to d_1 and d_3 species. The relative amounts of d_1 and d_3 present may be indicative of the relative ease of cleaving a C-H bond as opposed to the stronger C-D bond in (LXXXIVb). The d_0 species can arise from ion (LXXXIVc), while the d_2 species can be viewed as arising from both (LXXXIVc) and (LXXXIVa).

(2) Results and Discussion of System II

When 1,1-bis(hydroxymethyl)cyclohexane (LXXVII) was subjected to the 50% deuteriosulfuric acid reaction conditions, the same five products were obtained. Mechanism XI (p. 59, the allylic pathway mechanism adapted to deuteriosulfuric acid conditions) suggests the expected isotopic distribution of the 1-methyl-8-oxabicyclo[3.2.1] octane (LXIII) fraction to contain d_2, d_1 and d_0 species. The actual distribution indicates that none of these species are present and, in fact, the major contributors are d_{10} and d_{14} species (Table IV). The extensive exchange observed is not likely to have come about by way of carbonium ion (LXXXIV), since the cycloheptanecarboxaldehyde (LXXXI) fraction was not extensively deuterated, as shown by nmr analysis. It is possible that under acidic conditions the product (LXIII) may open to give some form of 1-methyl-1,4-cycloheptanediol (LXII), which can exchange through the olefins indicated in Mechanism XII ((LXII) is not a necessary intermediate, in as much as (LXIII) can give the indicated products directly.) Indeed, when 1-methyl-1,4-cycloheptanediol (LXII) was subjected to 35% deuteriosulfuric acid reaction conditions, 1-methyl-8-oxabicyclo[3.2.1]octane (LXIII) was obtained as the only steam-distillable product, the isotopic distribution of which (Table V) shows clearly a predominance of d_{10} and, to an appreciable extent, d_{14} species. Since the milder conditions employed here do not favor the formation of methyl cyclohexyl ketone (LXXIX) from 1,1-bis-(hydroxymethyl)cyclohexane (p 52), the failure to observe (LXXIX) here does not preclude its formation under more strenuous conditions

Mechanism XI





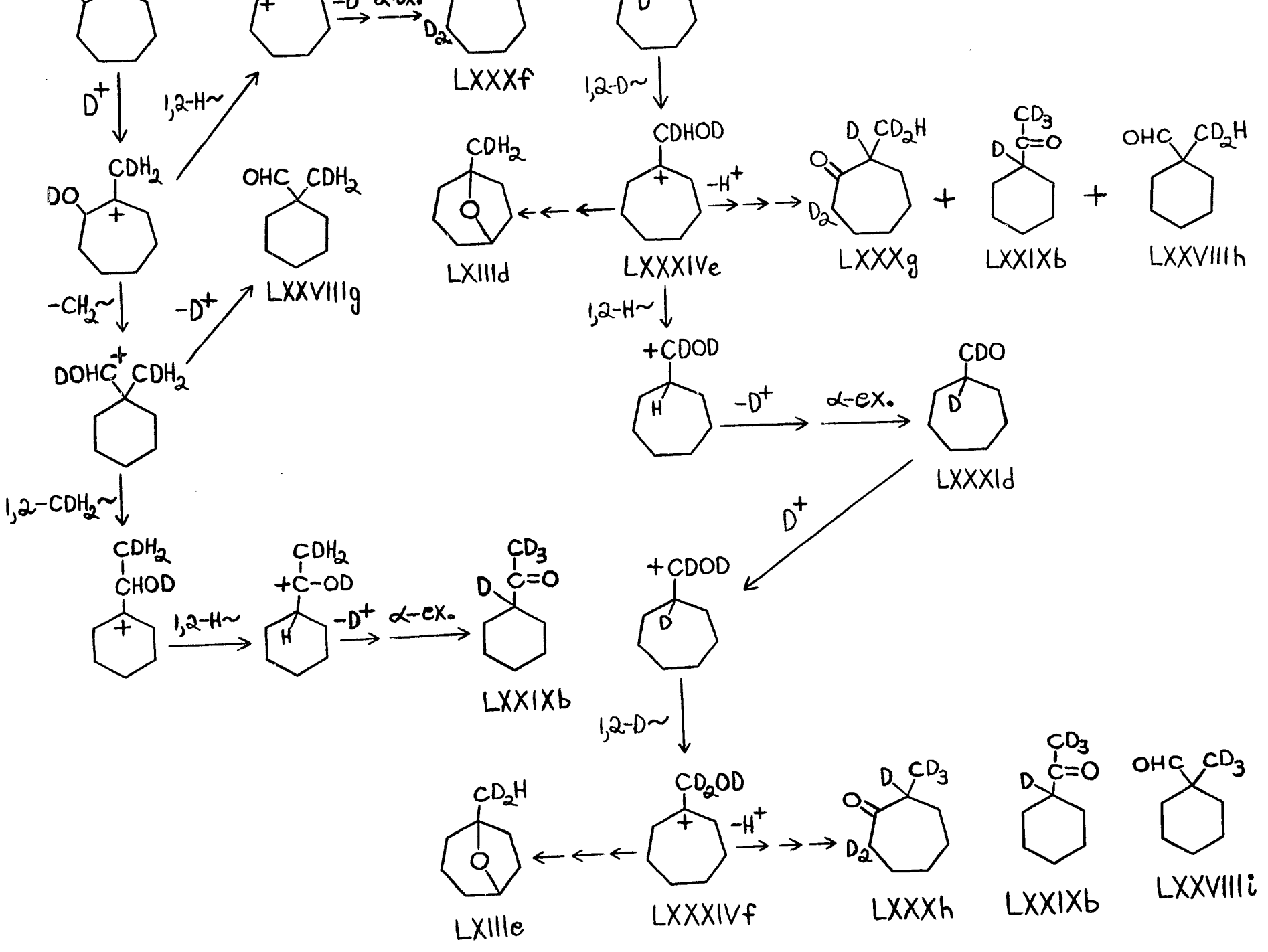
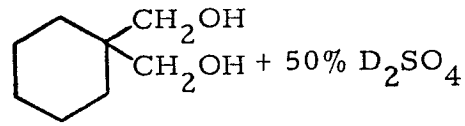
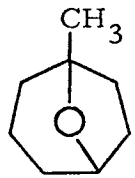
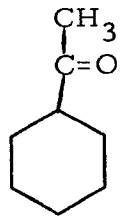
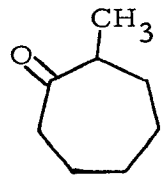


TABLE IV[a]

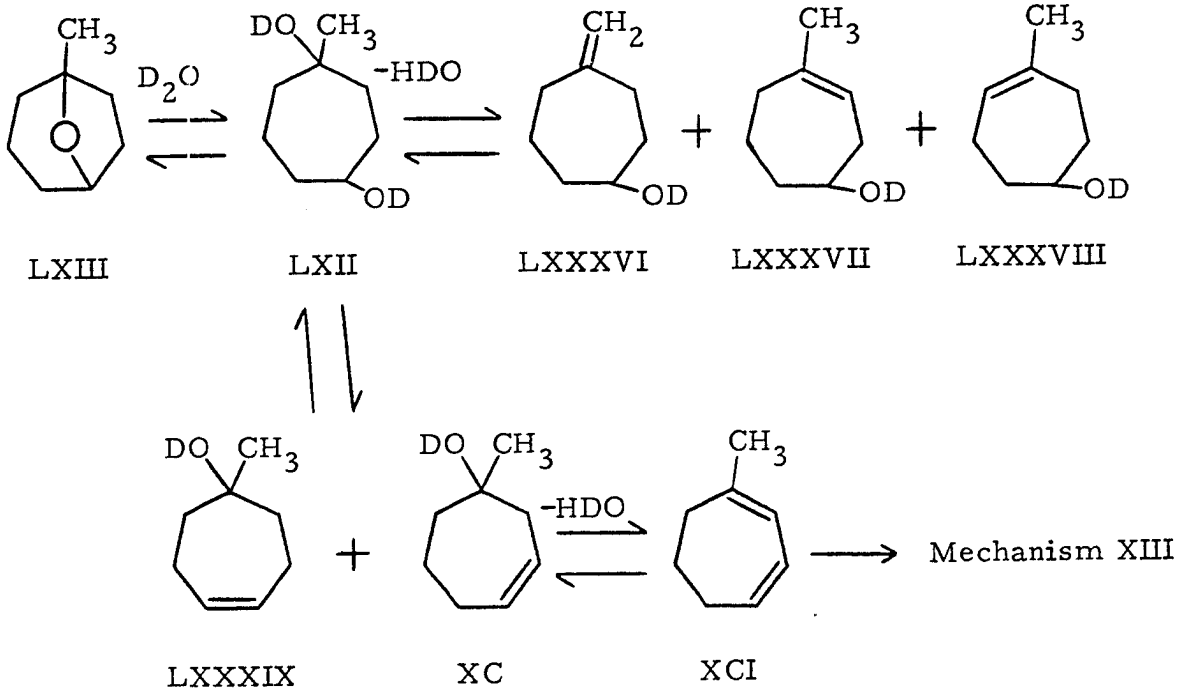


m/e (%)

Product	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140
	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}	d_{11}	d_{12}	d_{13}	d_{14}
 LXIII	-	-	-	-	-	-	0.2	0.4	1.5	5.5	22.0	7.3	7.7	16.5	39.0
 LXXIX	3.3	0.8	1.6	5.2	34.7	2.8	3.5	1.3	2.9	2.8	5.5	2.5	5.8	7.3	20.0
 LXXX	-	-	1.2	6.2	20.6	22.0	26.0	3.0	1.5	3.4	6.3	0.8	1.7	2.8	4.5

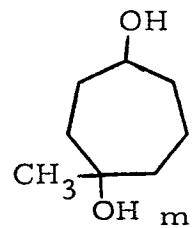
(a) Corrected for (M+1) contribution.

MECHANISM XII



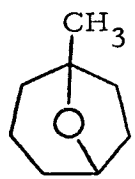
(see the discussion (p 66) of the isotopic distribution of the methyl cyclohexyl ketone (LXXIX) from 1, 1-bis-(hydroxymethyl)cyclohexane). Also, the relative amounts of d_{10} and d_{14} components obtained here cannot be accurately compared to those obtained from 1-1-bis-(hydroxymethyl)cyclohexane under the 50% deuteriosulfuric acid reaction conditions (Table IV, p 60), in as much as a 15% change in acid concentration could readily alter the relative contributions from both species. Since two distinct maxima in the isotopic distribution are observed here at d_{10} and d_{14}, as with the 1-methyl-8-oxabicycl[3. 2. 1]octane (LXIII) from 1, 1-bis-(hydroxymethyl)cyclohexane (p 60), it appears reasonable to consider the extensive exchange as coming about by way of two distinct

TABLE V[a]



+ 35% D_2SO_4

m/e (%)

Product	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140
	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}	d_{11}	d_{12}	d_{13}	d_{14}
 LXIII	3.6	3.4	4.0	5.0	6.8	7.5	6.5	6.0	2.3	7.3	25.1	3.9	3.7	5.5	9.4

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

pathways involving 1-methyl-1,4-cycloheptanediol (LXII).

Initial dehydration of 1-methyl-1,4-cycloheptanediol (LXII) would preferentially involve the tertiary hydroxyl function and, therefore, olefins (LXXXVI), (LXXXVII), and (LXXXVIII) would be the expected major products (Mechanism XII, p 61). In deuterated media, the reversible formation of these olefins would result in the incorporation of seven deuterium atoms into the 1-methyl-8-oxabicyclo[3.2.1] octane (LXIII) product. Involvement of the secondary hydroxyl function in dehydration of (LXII) would result in the formation of olefins (LXXXIX) and (XC) (Mechanism XII). The reversible formation of (LXXXIX) would, in deuterated media, result in the incorporation of three deuterium atoms into the ether (LXIII) product. Therefore, the generation of a d_{10} species can be accomplished by invoking the reversible formation of olefins (LXXXVI), (LXXXVII), (LXXXVIII), and (LXXXIX) (Mechanism XII, p 61). Loss of a second molecule of water from olefin (XC) would yield the conjugated diene (XCI). A series of consecutive 1,4-addition-eliminations of water[29] on this substituted butadiene (as shown in Mechanism XIII) is equivalent to having a conjugated diene migrate about the ring, a phenomenon which, in deuterated media, would result in the substitution of all ring hydrogens by deuteriums. A fast, reversible step (LXII)$\longrightarrow$(XC) (Mechanism XII) would necessitate the formation of an ether (LXIII) product intermediate in deuterium content to the d_{10} and d_{14} species observed. Since the contribution from d_{11}, d_{12}

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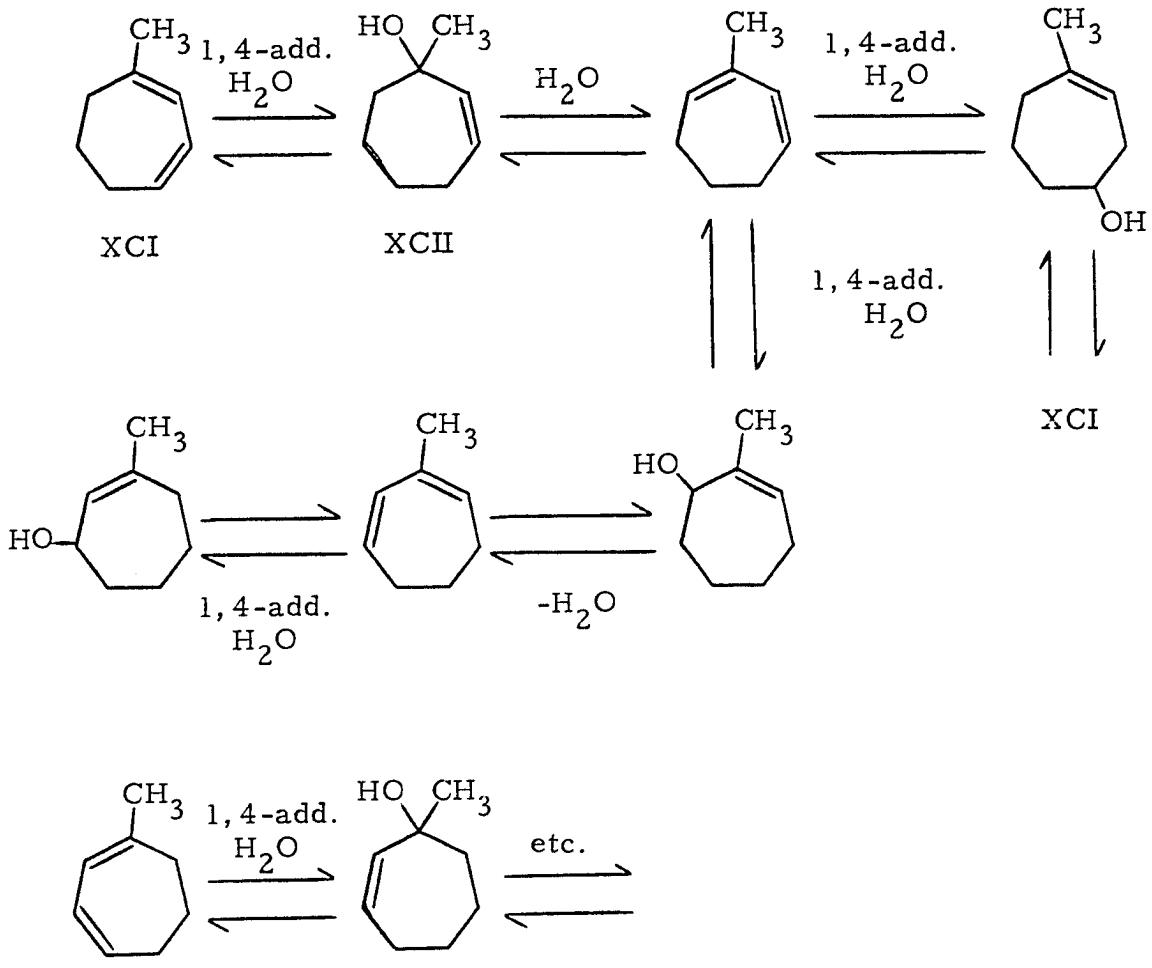
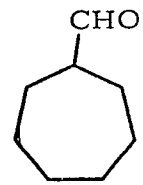
(29) A series of addition-eliminations of H^+ would serve the same purpose, in which case an alcohol need not be an intermediate.

MECHANISM XIII



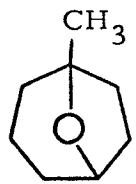
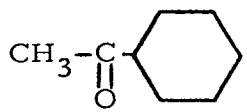
and d_{13} species is minimal (see Tables IV, V, and VI, p 60, p 62, and p 65), the above consideration suggests that step (XC) ⟶ (LXII) is slow relative to the formation of (XCI) from (XC) (Mechanism XII, p 61) and subsequent exchange (Mechanism XIII, above). A completely deuterated ether (LXIII) product can be pictured as arising from the exchange pathway (Mechanism XIII, above) by way of intermediate (XCIIa) (p 66).

TABLE VI[a]

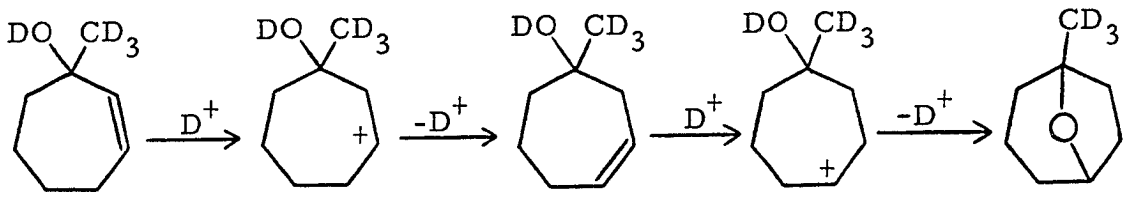


+ 50% D_2SO_4

m/e (%)

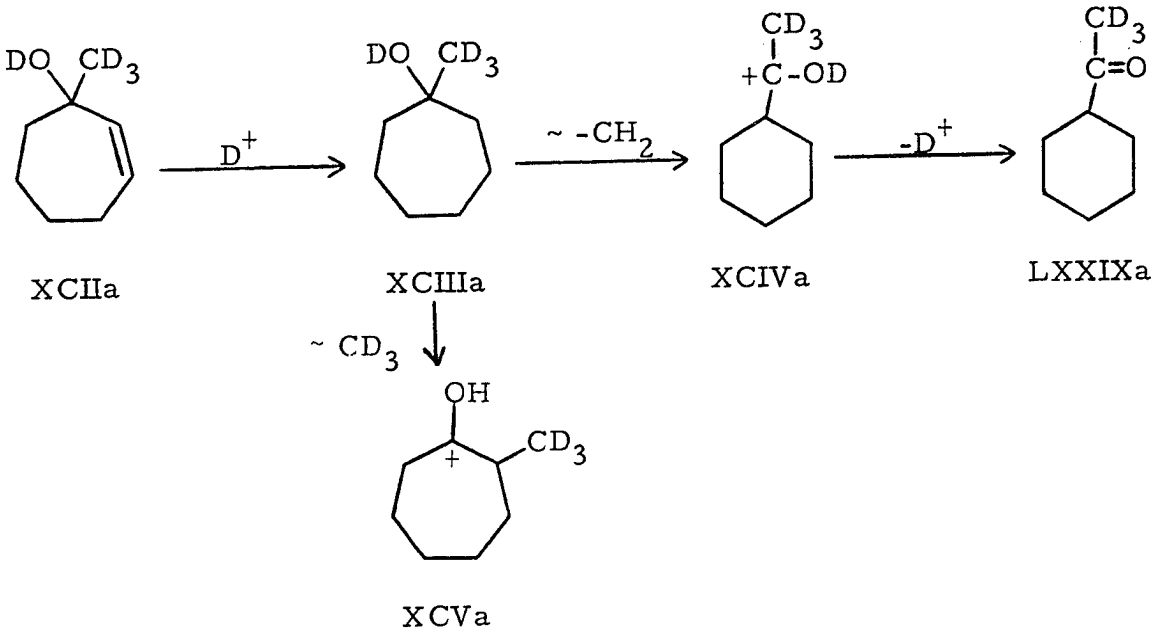
Product	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140
	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}	d_{11}	d_{12}	d_{13}	d_{14}
 LXIII	-	-	-	-	-	-	0.3	0.4	1.5	5.8	27.8	7.3	6.5	14.2	36.2
 LXXIX	0.4	0.4	1.5	12.0	47.6	2.5	1.5	0.4	0.7	1.6	3.7	1.8	4.0	7.9	14.0

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



XCIIa XCa LXIIIf

From Mechanism XI (p 59) the methyl cyclohexyl ketone (LXXIX) fraction obtained from the reaction of 1,1-bis-(hydroxymethyl)cyclohexane with 50% deuteriosulfuric acid should contain a d_4, alpha-exchanged system only. Nmr analysis shows an absence of alpha-hydrogen, while the isotopic distribution (Table IV, p 60) indicates that a d_4 system is indeed the major component. However, the completely exchanged, d_{14}, system is also present to a substantial extent (the slight peaking at d_{10} is considered insignificant, and probably represents some leakage from the exchange pathway leading to a d_{10} ether (LXIII) (p 63)). A completely deuterated methyl cyclohexyl ketone (LXXIX) product can arise from Mechanism XIII (p 64) by way of intermediate (XCIIa). Ring contraction involving ion (XCIIIa) would yield a protonated methyl cyclohexyl ketone (XCIVa). This consideration assumes that a ring contraction would be more favorable than a methyl shift, which would produce a protonated α-methylcycloheptanone (XCVa). This is not unreasonable, in as much as a ring contraction would cause relief of ring and torsional strain in the system. Since the α-methylcycloheptanone (LXXX) obtained from the reaction of



XCIIa XCIIIa XCIVa LXXIXa

XCVa

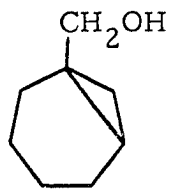
1,1-bis-(hydroxymethyl)cyclohexane with deuteriosulfuric acid is not extensively deuterated (see Table IV, p 60), there can be little methyl migration if ion (XCIIIa) is involved.

The possibility that Mechanism XIII (p 64) is involved in the formation of a completely deuterated methyl cyclohexyl ketone (LXXIX) from 1,1-bis-(hydroxymethyl)cyclohexane and deuteriosulfuric acid suggests that an appreciable amount of ketone (LXXIX) comes about by way of ring opening of the 1-methyl-8-oxabicyclo[3.2.1] octane (LXIII) product (see Mechanism XII, p 61). Since 1-methyl-1-4-cycloheptanediol (LXII) was not subjected to the 50% deuteriosulfuric acid reaction conditions (see discussion on p 58), this possibility cannot be ruled out.

Mechanism XI (p 59) indicated the expected isotopic distribution of the α-methylcycloheptanone (LXXX) fraction to be composed of d_4, d_5 and d_6 species. The actual distribution, Table IV, is in excellent

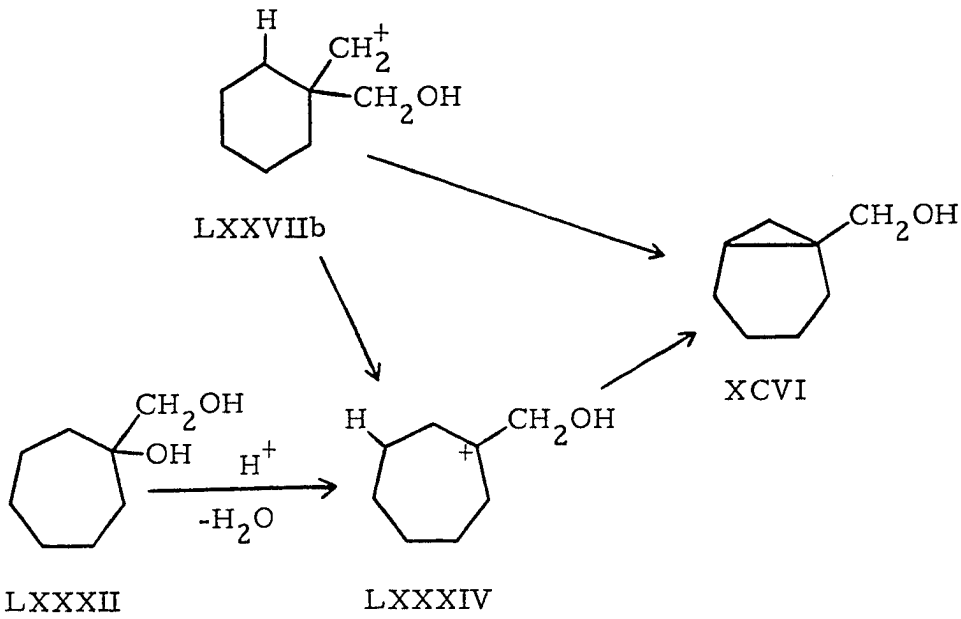
agreement with this prediction, there being a clear predominance of these three species. The slight peaking at d_{10} and d_{14} is considered insignificant (see discussion of methyl cyclohexyl ketone fraction (p 66)). On the basis of this and previous observations (see p 57), it is suggested that the α-methylcycloheptanone (LXXX) fraction arises mainly by way of an allylic-shift pathway (Mechanism XI).

By analogy with the 2, 2-dimethyl-1-3-propanediol system (p 25), it is important at this point to consider the possible intervention of 1-hydroxymethylbicyclo[4. 1. 0]heptane (XCVI), a cyclopropyl carbinyl system. Such a system can be formed either by a β-proton loss in the starting incipient primary carbonium ion (LXXVIIb) or by a

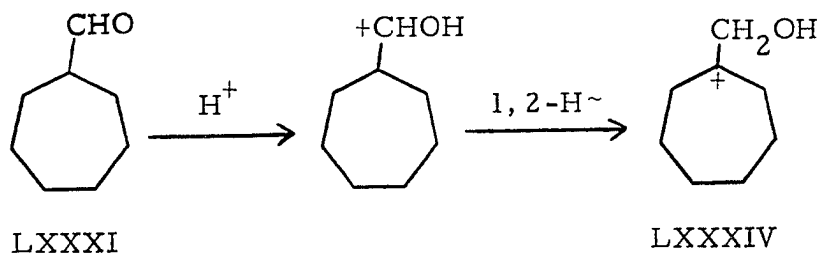


XCVI

β-proton loss in the ring expanded ion (LXXXIV). Since it is found that 1-hydroxymethylcycloheptanol (LXXXII) gives the same distribution of products as 1, 1-bis-(hydroxymethyl)cyclohexane (LXXVII) at various acid concentrations, it is likely that ion (LXXXIV) is a common intermediate, and, therefore, the more probable procursor for the desired cyclopropyl system (XCVI), is indeed (XCVI) is an intermediate. The isotopic distributions of the 1-methyl-8-oxabicyclo[3. 2. 1]octane (LXIII) and the methyl cyclohexyl ketone (LXXIX) fractions obtained from the



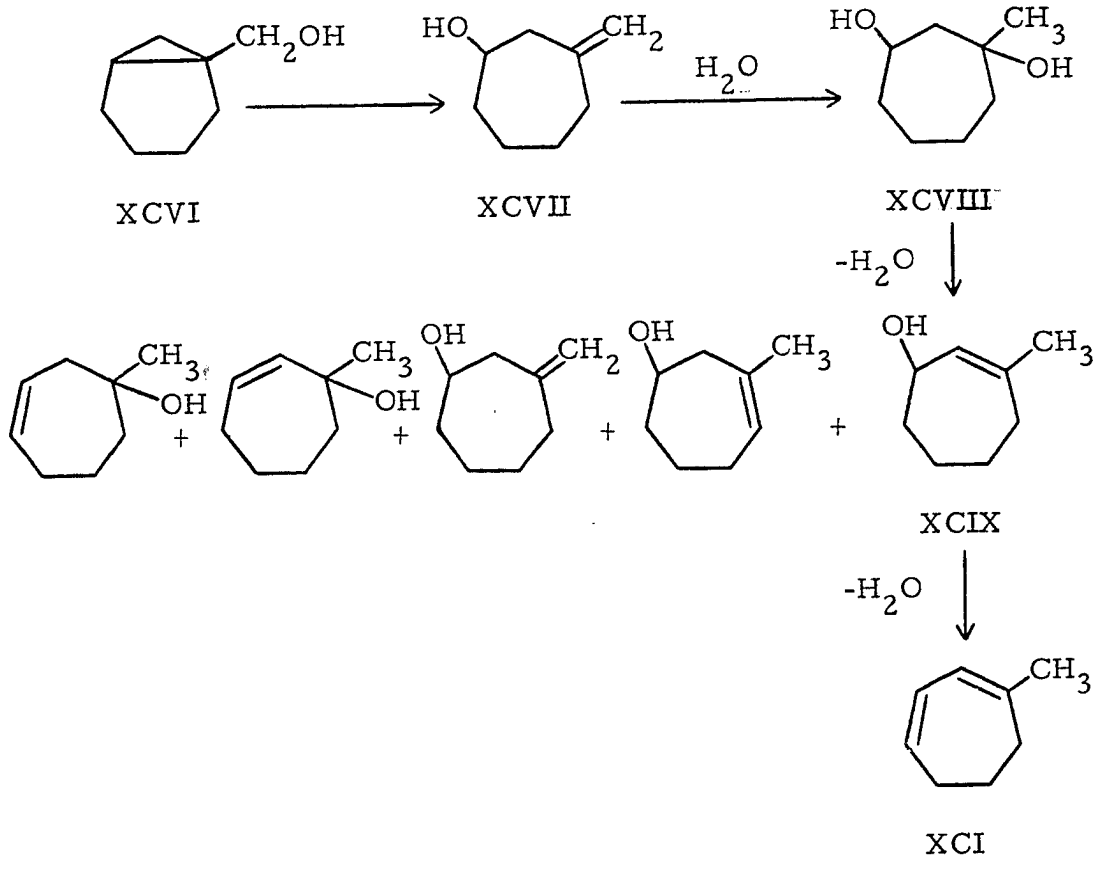
reaction of cycloheptanecarboxaldehyde (LXXXI) with 50% deuteriosulfuric acid (Table VI, p 65) are similar to those observed for the reaction of 1,1-bis-(hydroxymethyl)cyclohexane (LXXVII) with 50% deuteriosulfuric acid (Table IV, p 60), again suggesting the intermediacy of (LXXXIV).



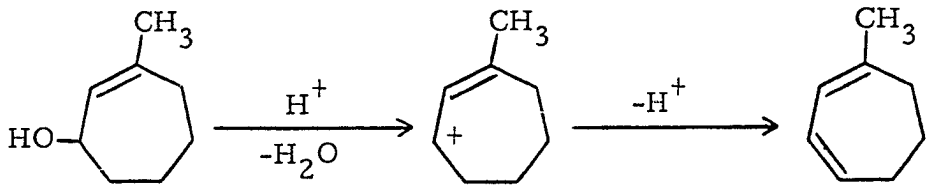
The probable mode of rearrangement of 1-hydroxymethylbiclo-[4.1.0]heptane (XCVI) is outlined in Mechanism XIV. The initial rearrangement, step (XCVI) ⟶ (XCVII), is a cyclopropylcarbinyl to

allylcarbinyl isomerization, analogous to that discussed in connection with the 2,2-dimethyl-1,3-propanediol system (p 30). The homoallylic alcohol (XCVII) would be expected to hydrate readily to give (XCVIII), an analog of 3-methyl-1,3-butanediol (XLVII). Stepwise dehydration of (XCVIII) would result in the formation of diene (XCI), the system considered in connection with the complete deuteration of the 1-methyl-8-oxabicyclo[3.2.1]octane (LXIII) product from 1-methyl-1,4-cycloheptanediol (LXII) (p 63). The difference here is that to the extent that Mechanism XIV participates, that portion of the product from 1,1-bis-(hydroxymethyl)cyclohexane (LXXVII) can be accounted for

MECHANISM XIV



without invoking a 1, 5-hydrogen transfer process (see Mechanism XI, p 59, for the proposed 1, 5-hydrogen transfer process). Initial dehydration of (XCVIII) would favor formation of the allylic alcohol (XCIX), which could now undergo a second facile dehydration, through allylic carbonium ion (C), to give (XCI). 1-Methyl-1, 4-cycloheptanediol (LXII)



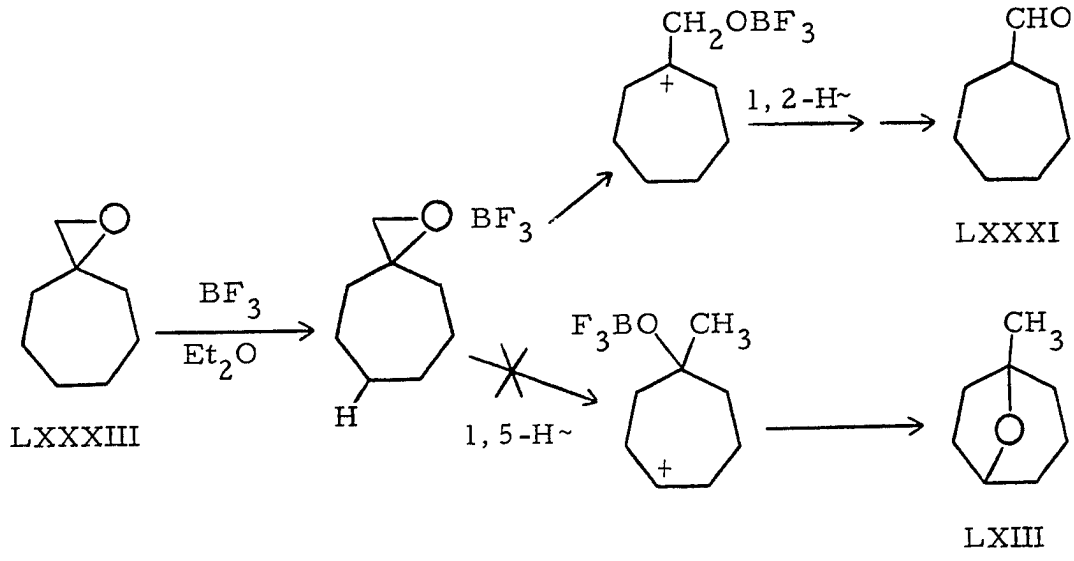
XCIX C XCI

cannot give an allylic alcohol upon initial dehydration and, therefore, further dehydration to a substituted butadiene system would not be as favorable in this case. Since the 1, 4-diol (LXII) does give a completely deuterated 1-methyl-8-oxabicyclo[3. 2. 1]octane (LXIII) (Table V, p 62) it is necessary to consider both the ether (LXIII) product itself (Mechanism XII, p 61) and the cyclopropyl carbinol (XCVI) (Mechanism XIV, p 70) as possible precursors to the substituted butadiene (XCI) system, if indeed (XCI) is responsible for the completely deuterated 1-methyl-8-oxabicyclo-[3. 2. 1]octane (LXIII) and methyl cyclohexyl ketone (LXXIX) observed from the reaction of 1, 1-bis-(hydroxymethyl)cyclohexane (LXXVII) with deuteriosulfuric acid (Table IV, p 60).

In as much as the rather harsh conditions employed here appear to favor multi-step exchange processes, a more elegant demonstration of the role of a 1, 5-hydrogen transfer route in the formation of 1-methyl-8-oxabicyclo[3. 2. 1]octane (LXIII), by means of deuterium labeling, is

not feasible. As a result, attempts were made to effect this transfer under much milder conditions. The reaction of 8-oxaspiro[2.6]nonane (LXXXIII) with boron trifluoride has been reported to give a 90% yield of cycloheptanecarboxaldehyde (LXXXI) (Mechanism XV).[30] This reaction was rerun with the hope of finding (LXIII) amongst the 10% of unidentified product. A 93% yield of cycloheptanecarboxaldehyde (LXXXI)

MECHANISM XV



was obtained, but glc analysis did not reveal the formation of any 1-methyl-8-oxabicyclo[3.2.1]octane (LXIII). Evidently, the solvent and temperature conditions employed here render a 1,5-hydrogen transfer process energetically unfavorable. In the poorer solvating medium, ether, the course of the reaction may well be dictated by the relative

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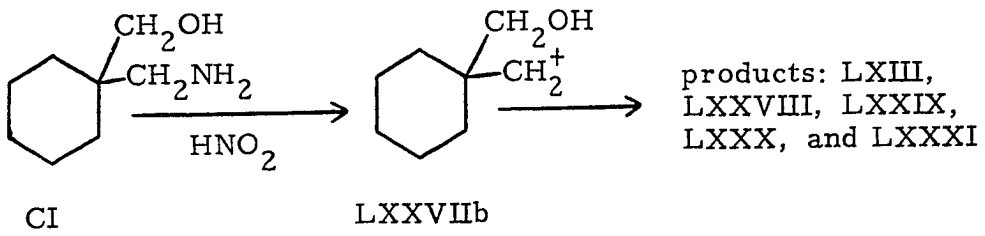
(30) E. J. Corey and M. Chaykovsky, J. Amer. Chem. Soc., 87, 1358 (1965).

stability of a tertiary carbonium ion as compared to a secondary carbonium ion.

The nitrous acid deamination of 1-aminomethyl-1-hydroxymethylcyclohexane (CI) was investigated in an attempt to generate,



CI LXXVIIb

under very mild conditions, the primary carbonium ion (LXXVIIb), which is postulated to rearrange to products (LXIII), (LXXVIII), LXXIX),(LXXX), and (LXXXI), under strongly acidic conditions. The reaction gave a pale yellow solid, the nmr and ir spectra of which revealed no methyl or carbonyl functions. The spectra were highly suggestive of a saturated diol.

In conclusion, it was found that of those conditions employed, only those of reasonable acidity and high temperature gave rearrangement products, and these were inevitably accompanied by rapid proton exchange processes, with no evidence of 1,3-hydride transfer.

EXPERIMENTAL

Microanalysis was performed by Galbraith Microanalytical Laboratory, Knoxville 21, Tennessee.

Melting points were determined on a Thomas-Hoover apparatus and are corrected; boiling points are uncorrected.

Gas-liquid chromatography was performed on a Microtek Model GC 2500 R (analytical work) or on an Aerograph Model A-700 (preparative work).

Mass spectra were determined on a CEC 21-103C Mass Spectrometer by Esso Research Laboratories, Linden, New Jersey (dimethyl system) or on a Hitachi RMU-6 by Morgan-Schaffer, Montreal, Canada (cyclohexane system).

Other spectra were taken on the following instruments: infrared, Perkin-Elmer 137 (absorption maxima are expressed in reciprocal centimeters); nuclear magnetic resonance, Varian A-60 (chemical shifts are expressed in ppm (δ) downfield from internal tetramethylsilane ($\delta = 0$)).

(A) Preparation of 1-Aminomethyl-1-hydroxymethylcyclohexane (CI)[31]

(1) Preparation of 1-Cyano-1-carbethoxycyclohexane[32]

Sodium (29.9g, 1.3 mol) was added cautiously to 350 ml of absolute ethanol in a 2-l. three-necked flask equipped with a mechanical stirrer, a 1-l. pressure equalizing addition funnel, and a reflux condenser containing a drying tube. The resulting mixture was stirred until solution was effected, after which time 146.9g (1.3mol) of ethyl cyanoacetate were added. After stirring for 15 min, 303g (1.3 mol) of 1,5-dibromopentane were rapidly added. The resulting solution was heated under reflux for 14 hr, cooled and diluted with 400 ml of absolute ethanol. Sodium (29.9g, 1.3mol) was added as above, and this was followed by heating at reflux for an additional 24 hr. After cooling to room temperature, the resulting red suspension was filtered, and concentrated (rotary evaporator) to a final volume of approximately 500 ml. This material was washed with 1-500 ml portion of water and extracted with 3-700 ml portions of ether. Drying with $MgSO_4$, filtration, and evaporation of the solvent gave a clear, red oil which was distilled under reduced pressure to yield 74.3g (32%) of a clear, colorless oil: bp 105-108° (4.8 mm) (lit[31] bp 95-97° (2-3 mm)); nmr ($CDCl_3$):δ 1.30 (sharp triplet, CH_3), δ 1.8 (broad multiplet, ring CH_2), δ 4.28 (sharp quartet, O-CH_2); ir (liquid film):2930, 2850 (s, alkyl-H),

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(31) H. Najer, R. Giudicelli, J. Sette, and J. Menin, Bull. Soc. Chim. Fr., 204 (1965)

(32) W. J. Bailey, J. Amer. Chem. Soc., 81, 5397 (1959).

2240 (w, nitrile), 1750 (s, ester).

(2) Preparation of 1-Aminomethyl-1-hydroxymethylcyclohexane (CI)[31]

Lithium aluminum hydride (9.0g, 0.24 mol) and 100 ml of anhydrous ether were placed in a 250-ml three-necked flask equipped with a mechanical stirrer, a 25-ml pressure equalizing addition funnel, and a reflux condenser containing a drying tube. 1-Cyano-1-carbethoxycyclohexane (20.0g, 0.11 mol) was added dropwise to the stirred suspension at such a rate as to maintain gentle refluxing. The addition took 2.5 hr. The final mixture was heated at reflux for 1.5 hr, after which time the reaction flask was immersed in an ice-water bath, and the aluminum salts were decomposed by the dropwise addition of 160 ml of water. The resulting material was extracted with 4-200 ml portions of ether. Drying with $MgSO_4$, filtration, and evaporation of the solvent gave a clear, very viscous oil which was distilled under reduced pressure to yield 9.4g (61.5%) of a clear, very viscous oil which solidified on standing: bp 138.5-139° (11.2 mm), mp 39-40° (lit[31] bp 86° (1-2 mm), mp 39.5°); nmr ($CDCl_3$): δ 1.40 (broad singlet, ring CH_2), δ 2.80 (broad, unresolved doubled, N-CH_2 and NH_2, OH), δ3.60 (sharp singlet, O-CH_2); ir (liquid film): 3300 (s, OH, NH_2), 2920, 2860 (s, alkyl-H), 1600 (m, NH_2), 1040 (s, primary alcohol).

(B) Preparation of 1, 1-Bis-(hydroxydeuteriomethyl)cyclohexane (LXXVIIa)[33]

Lithium aluminum deuteride (6.0g, 0.144 mol) and 80.0 ml of anhydrous ether were placed in a 250-ml three-necked flask equipped with a mechanical stirrer, a 25-ml pressure equalizing addition funnel, and a reflux condenser containing a drying tube. Diethyl 1, 1-cyclohexanedicarboxylate (26.3g, 0.115 mol) was added dropwise to the stirred suspension at such a rate as to maintain gentle refluxing. The addition took 3.5 hr. The final mixture was heated at reflux for 3.0 hr, after which time the reaction flask was immersed in an ice-water bath, and the excess $LiAlD_4$ was decomposed by the dropwise addition of 15 ml of water, followed by 50 ml of 10% HCl. The resulting mixture was extracted with 5-100 ml portions of ether. Drying with $MgSO_4$, filtration, and evaportation of the solvent gave a white, crystalline solid, which was slurried in benzene and filtered to yield 9.7g (57%) of the diol as white needles: mp 92.5-94.5° (lit[33] (undeuterated diol) mp 97.5-98.5°); nmr ($CDCl_3$): δ 1.42 (broad singlet, ring CH_2), δ 2.70 (broad singlet, OH).

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(33) Patterned after E. R. Buchman, D. H. Deutsch, and G. I. Fujimoto, J. Amer. Chem. Soc., 75, 6228 (1953).

(C) Preparation of Cycloheptanecarboxaldehyde (LXXXI)[30]

(1) Preparation of 1-Oxaspiro[2.6]nonane (LXXXIII)[30]

Cycloheptanone (68.8 ml, 0.61 mol), trimethyl sulfonium iodide (200g, 0.91 mol), and 75 ml of dimethyl sulfoxide were placed in a 3-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a 1-l. pressure equalizing addition funnel. The mixture was stirred under nitrogen for 20 min, resulting in the formation of a milky-white suspension. A solution of potassium tert-butoxide (91.91g, 0.91 mol) in 400 ml of dimethyl sulfoxide was added dropwise, under nitrogen, over a period of 1.5 hr, the reaction flask being immersed in a cold water bath during the addition. The resulting cloudy, yellow-orange mixture was allowed to remain at room temperature overnight, after which time it was cautiously treated with approximately 2 l. of water, while being stirred in an ice-water bath. Extraction with 7-350 ml portions of ether, drying with $MgSO_4$, filtration, and evaporation of the solvent gave a clear, yellow oil which was distilled under reduced pressure to yield 60.1g (78%) of a clear, colorless oil: bp 83-85° (20 mm) (lit[30] bp 63° (14 mm)); nmr (CCl_4): δ1.62 (sharp singlet, 12H, ring CH_2), δ2.41 (sharp singlet, 2H, epoxy CH_2); ir (liquid film): 3050 (m, epoxy CH_2), 2930, 2860 (s, alkyl-H), 1450 (m, ring CH_2).

(2) Preparation of Cycloheptanecarboxaldehyde (LXXXI)[30]

A solution of 1-oxaspiro [2.6] nonane (LXXXIII) (19.7g, 0.16 mol) in 500 ml of anhydrous ether was placed in a 1-l. one-necked flask immersed in an ice-water bath. A solution of boron trifluoride etherate (10.0 ml) was added rapidly to the stirred solution, and the resulting mixture was heated under reflux for 0.5 hr. The reaction mixture was washed with 2-100 ml portions of 10% $NaHCO_3$ solution. Drying with $MgSO_4$, filtration, and evaporation of the solvent gave a clear, pale yellow oil, which was distilled under reduced pressure to yield 18.0g (91%) of the aldehyde as a clear, colorless oil: bp 85-86° (30 mm) (lit[34] bp 74° (25 mm)); nmr (CCl_4): δ 1.57 (broad singlet, ring CH_2), δ 2.22 (broad multiplet, methine), δ 9.22 (sharp singlet, aldehyde H).

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(34) M. Finkelstein, Chem. Ber., 90, 2097 (1957).

(D) Preparation of Deuteriosulfuric Acid[35]

Deuterium oxide (228 ml, 99.8%) was placed in a 2-l. one-necked flask equipped with a 1-l. pressure equalizing addition funnel. The flask was immersed in a dry ice-acetone bath, and 470 ml of Sulfan (Baker and Adamson, stabilized liquid sulfur trioxide) were added dropwise over a period of 2.5 hr. The rate of addition could be increased toward the end. After the addition was complete, the contents of the flask were allowed to warm to room temperature overnight. The resulting clear, viscous liquid was considered to be 100% deuteriosulfuric acid by calculation. Nmr analysis showed it to be better than 99.5% D.

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(35) E. F. Denny and J. D. Roberts, J. Amer. Chem. Soc., 78, 2008 (1956).

(E) Preparation of 2, 2-Dimethylcyclopropanol (XXIV)[36]

(1) Preparation of β-Chloroethyl Formate[37]

Benzene (500 ml) was placed in a 2-l. one-necked flask equipped with a magnetic stirrer, and a Dean-Stark trap with condenser. 2-Chloroethanol (160g, 2 mol), 90% formic acid (100 ml, 2 mol), and p-toluenesulfonic acid (2g) were added to the flask with rapid stirring, and the resulting mixture was heated at reflux until no more water was collected (1.5 hr). The clear benzene solution was washed with 1-l. of saturated $NaHCO_3$ solution. Drying with $MgSO_4$, filtration, and distillation of the solvent gave a clear, orange liquid which was further distilled to yield 83.5g (40%) of a clear, colorless oil: bp 129.5-131.5° (760 mm) (lit[37] bp 129-132° (760 mm)); nmr ($CDCl_3$): δ3.75 (2H) and δ4.43 (2H)(multiplets, CH_2), δ 8.13 (sharp singlet, 1H, formate H).

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(36) U. Schollkopf, J. Paust, A. Al-Azrak, and H. Schumacher, Chem. Ber., 99, 3391 (1966).

(37) H. Baganz and L. Damaschke, Chem. Ber., 91, 653 (1958).

(2) Preparation of Dichloromethyl β-Chloroethyl Ether[38]

Phosphorus pentachloride (142.0g, 0.68 mol) was placed in a 250-ml three-necked flask equipped with a mechanical stirrer, a 25-ml pressure equalizing addition funnel, and a drying tube. β-Chloroethyl formate (82.0g, 0.76 mol) was added dropwise over a period of 0.5 hr, while the reaction flask was immersed in an ice-water bath. The resulting pale-yellow suspension was allowed to warm to room temperature over a period of 1 hr, during which time a clear, pale-yellow solution was formed. The final solution was distilled under reduced pressure to yield 94.3g (76%) of a clear, colorless liquid: bp 109-114° (115 mm) (lit[38] bp 106-110° (110 mm)); nmr ($CDCl_3$): δ 3.75 (2H) and δ 4.25 (2H) (multiplets, CH_2), δ7.37 (sharp singlet, IH, methine).

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(38) Patterned after H. Gross, A. Rieche, and E. Höft, Chem. Ber., 94, 544 (1961).

(3) Preparation of β-Chloroethyl 2,2-Dimethylcyclopropyl Ether[36]

Dichloromethyl β-chloroethyl ether (40.0g, 0.25 mol) and isobutylene (500 ml, 9.0 mol) were placed in a 2-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser (Dewar type, containing dry ice-acetone mixture), and a 1-l. pressure equalizing addition funnel. A solution of methyllithium-lithium iodide[39] (5.0% in diethyl ether, 320 ml, 0.5 mol) was added dropwise to the vigorously stirred solution over a period of 3 hr. After slowly warming to room temperature overnight, the resulting white suspension was treated with 100 ml of water. Extraction with 3-100 ml portions of ether, drying with $MgSO_4$, filtration, and distillation of the solvent gave a clear, yellow oil which was distilled under reduced pressure to yield 28.7g (77%) of a clear, colorless liquid: bp 67-72°(20 mm) (lit[36] bp 50-53° (14 mm)); nmr ($CDCl_3$): δ 0.35 (multiplet, ring CH_2), δ 0.98 and δ 1.15 (sharp singlets, CH_3), δ 3.03 (multiplet, methine), δ 3.67 (multiplet, CH_2).

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(39) H. Gilman, E. A. Zoellner, and W. M. Selby, J. Chem. Soc., 55, 1252 (1933).

(4) Preparation of 2, 2-Dimethylcyclopropanol (XXIV)[36]

A solution of β-chloroethyl 2, 2-dimethylcyclopropyl ether (10.0g, 0.07 mol) in 25 ml of anhydrous ether was placed in a 500-ml three-necked flask equipped with a mechanical stirrer, a 150-ml pressure equalizing addition funnel, and a reflux condenser containing a drying tube. A solution of ethyllithium-lithium bromide[39] (7.0% in diethyl ether, 145 ml, 0.25 mol) was added dropwise to the vigorously stirred solution over a period of 20 min. The resulting white suspension was treated with 150 ml of 5% $NaHCO_3$ solution, while the reaction flask was immersed in an ice-water bath. Extraction with 4-50 ml portions of ether, drying with Na_2SO_4, filtration, and distillation of the solvent gave a clear, colorless oil which was distilled (bp 41-44° (16 mm) (lit[36] bp 42° (14 mm)) to yield 3.0 g of a mixture which nmr analysis revealed to contain 70% of 2, 2-dimethyl-cyclopropanol (XXIV) and 30% of starting material. The cyclopropanol was extracted into D_2O and used as such for further reaction; nmr (cyclopropanol contribution)(neat mixture): δ 0.35 (multiplet, ring CH_2), δ 0.97 and δ 1.17 (sharp singlets, CH_3), δ 3.10 (multiplet, methine), δ 4.72 (singlet, OH).

(F) Preparation of 2,2-Dimethyl-1,1,3,3-tetradeuterio-1,3-propanediol (Xa)[40]

(1) Preparation of Diethyl-α,α-dimethyl malonate[41]

Sodium (15.8g, 0.7 mol) was added cautiously to 655 ml of absolute ethanol in a 3-l. three-necked flask equipped with a mechanical stirrer, a 150-ml pressure equalizing addition funnel, and a Claisen adapter containing a reflux condenser with a drying tube and a thermometer. The resulting mixture was stirred until solution was effected, after which time 120g (0.75 mol) of diethylmalonate were added. After stirring for 10 min, 125g (0.9 mol) of methyl iodide was added at such a rate as to maintain the temperature at 20°, while the reaction flask was immersed in an ice-water bath. The resulting solution was heated under reflux for 0.5 hr, cooled, and diluted with 655 ml of absolute ethanol. Sodium (16.0g, 0.7 mol) and methyl iodide (125g, 0.9 mol) were added as above, and this was followed by heating at reflux for an additional 1.5 hr. After cooling to room temperature, the resulting suspension was filtered, and concentrated (rotary evaporator) to a final volume of approximately 800 ml. This material was mixed with 600 ml of water, and the organic layer which resulted was extracted with 5-350 ml portions of ether. Drying with $MgSO_4$, filtration, and evaporation of the solvent gave a clear, red oil which was distilled under reduced

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(40) Patterned after E. Testa and L. Fontanella, J. Org. Chem., 24, 1932 (1959).

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

pressure to yield 55.5g (40%) of a clear, colorless oil: bp 89-92° (16 mm) (lit[41] bp 193-195° (760 mm)); nmr ($CDCl_3$): δ 1.27 (sharp triplet, ethyl-CH_3), δ 1.41 (sharp singlet, geminal-CH_3), δ 4.22 (sharp quartet, ethyl-CH_2); ir (liquid film): 2970, 2930 (s, alkyl-H), 1750, 1730 (s, ester), 1380 (s, doublet, gem-CH_3).

(2) Preparation of 2, 2-Dimethyl-1, 1, 3, 3-tetradeuterio-1, 3-propanediol (Xa)[40]

Lithium aluminum deuteride (2.0g, 0.048 mol) and 21 ml of anhydrous ether were placed in a 50-ml three-necked flask equipped with a mechanical stirrer, a 25-ml pressure equalizing addition funnel, and a reflux condenser containing a drying tube. Diethyl-α-α-dimethylmalonate (7.2g, 0.038 mol) was added dropwise to the stirred suspension at such a rate as to maintain gentle refluxing. The addition took 1.5 hr. The final mixture was heated at reflux for 2.5 hr, after which time the reaction flask was immersed in an ice-water bath, and the excess $LiAlD_4$ was decomposed by the dropwise addition of 12 ml of water, followed by 20 ml of 15% HCl. The resulting mixture was extracted with 5-50 ml portions of ether. Drying with $MgSO_4$, filtration, and evaporation of the solvent gave a pale-yellow solid (3.5g), which was slurried in benzene and filtered to yield 2.5g (63%) of the diol as white needles: mp 121.5-124.5° (lit[40] (undeuterated diol) mp 125-127°); nmr ($CDCl_3$): δ 0.88 (sharp singlet, CH_3), δ 3.96 (singlet, OH).

(G) Preparation of 1-Hydroxymethylcycloheptanol (LXXXII)[42]

1-Oxaspiro[2.6]nonane (LXXXIII) (8.8g, 0.07 mol) and 10% NaOH solution (45 ml) were placed in a 100-ml one-necked flask equipped with a magnetic stirrer and a reflux condenser. The vigorously stirred mixture was heated at reflux for three days, cooled, and extracted with 6-50 ml portions of methylene chloride. Drying with $MgSO_4$, filtration, and evaporation of the solvent gave a yellow-orange solid which was recrystallized from hexane to yield 3.6g (36%) of the diol as white crystals: mp 52-52.5° (lit[43] mp 50-51°); nmr ($CDCl_3$) : δ 1.54 (broad singlet, ring CH_2) δ 3.40 (singlet, O-CH_2), δ 3.52 (singlet, disappears on shaking with D_2O, OH).

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(42) Patterned after R. U. Lemieux and R. K. Kullnig, J. Amer. Chem. Soc., 80, 2237 (1958).

(43) R. Blicke and C. Azuara, ibid., 75, 5418 (1953).

(H) Preparation of 3-Methyl-1,3-butanediol (XLVII)[44]

A sulfuric acid solution (5%, 80 ml) was placed in a 100 ml one-necked flask equipped with a magnetic stirrer and a reflux condenser. 3-Methyl-3-buten-1-ol (XXXII) (4.0g, 0.047 mol) was rapidly added to the preheated (100°), vigorously stirred solution. The reaction mixture was stirred for 5 min, after which time the reaction flask was immersed in an ice-water bath, and K_2CO_3 was added until neutralization was effected. The water was evaporated under vacuum at 60° to give a wet, crystalline solid which was extracted with 2-50 ml portions of ether. Drying with $MgSO_4$, filtration, and evaporation of the solvent gave 2.5g (50%) of a clear, colorless oil, which was shown by nmr analysis to contain no vinyl hydrogen; nmr (CD_3COCD_3): δ 1.23 (sharp singlet, 6H, CH_3), δ 1.73 (triplet, 2H, CH_2), δ 3.76 (triplet, 2H, O-CH_2), δ 4.45 (sharp singlet, OH). Preparative glc (DC550, 20% on 60/80 mesh chromosorb P, 60 cc of helium per min, 135°) gave two major components. One was found to have an nmr spectrum identical with that of an authentic sample of 3-methyl-3-buten-1-ol (XXXII) (a dehydration product of the diol (XLVII)). The other component gave an nmr spectrum identical with that described above, except in the region of δ 3.2-4.1. Here, three broad peaks were observed. However, when the sample was exposed to HCl vapors the spectrum became identical, in all respects, with that described above. This result indicates that the

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(44) K. M. Trenke, M. S. Nemtsov, and M. M. Kiseleva, Zh. Org. Khim. (Eng. Transl.), 3, 1327 (1967).

glc-pure diol (XLVII) is incapable of exchange, and, therefore, further coupling is observed in the nmr spectrum. The three peaks are the tertiary-OH (δ3.30), the O-CH_2 (broad triplet, δ 3.76), and the primary-OH (δ4.05)(to which coupling is taking place).

(J) Preparation of 1-Methylcyclobutanol (XXX)[45]

A solution of methyllithium (5.08% in diethyl ether, 50 ml, 0.08 mol) was placed in a 100-ml three-necked flask equipped with a mechanical stirrer, a 25-ml pressure equalizing addition funnel, and a reflux condenser containing a drying tube. A solution of cyclobutanone (5.0g, 0.07 mol) in 25 ml of anhydrous ether was added dropwise to the stirred solution over a period of 1.5 hr. The white suspension which formed was hydrolyzed by the dropwise addition of 25 ml of water to the cooled reaction mixture. The resulting two layers were separated, and the aqueous layer was extracted with 3-50 ml portions of ether. Drying with $MgSO_4$, filtration, and distillation of the solvent gave a clear, yellow-green oil which was further distilled to yield 2.7g (46%) of a clear, colorless oil: bp 116-117° (760 mm) (lit[45] bp 118-119° (760 mm)); nmr ($CDCl_3$): δ1.35 (sharp singlet, CH_3), δ2.0 (complex multiplet, ring CH_2), δ3.3 (sharp singlet, OH).

(45) J. D. Roberts, J. Amer. Chem. Soc, 78, 3222 (1956).

(K) Preparation of 1-Methylcyclopropylcarbinol (XXV)[46]

Zinc-copper couple (113g, 1.7 mol), iodine (15g), and anhydrous ether (450 ml) were placed in a 1-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser containing a drying tube, and a Claisen adapter containing two 150-ml pressure equalizing addition funnels. To the stirred suspension, methylene iodide (67 ml, 0.46 mol) and 2-methyl-2-propen-1-ol (51g, 0.70 mol) were added simultaneously at such a rate as to maintain gentle refluxing. The addition took 1.5 hr. The resulting gray-black suspension was heated at reflux for an additional 6.5 hr, cooled, and filtered to give a clear, pale-yellow filtrate. This material was washed with 5-100 ml portions of 5% HCl, followed by 10-100 ml portions of 5% $NaHCO_3$ solution. The ether solution was dried over $MgSO_4$, filtered, and the solvent removed by distillation. The resulting clear, yellow oil was distilled to yield 24.4g (60%) of a clear, colorless oil: bp 124-127° (760 mm) (lit[47] bp 126° (739 mm)); nmr ($CDCl_3$): δ 0.34 (multiplet, 4H, ring CH_2), δ 3.37 (broad singlet, 2H, hydroxyl methylene), δ4.17 (broad singlet, 1H, OH).

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(46) Patterned after H. E. Simmons and R. D. Smith, ibid., 80, 5323 (1958).

(47) E. F. Cox, M. C. Caserio, M. C. Silver, and J. D. Roberts, ibid., 83, 2723 (1961).

(L) Preparation of 1-Methyl-8-oxabicyclo[3.2.1]octane

(1) Preparation of 1,4-Cyclohexanediol Monobenzoate[48]

Pyridine (490 ml, 6.2 mol, dried over NaOH) and chloroform (700 ml, freed from alcohol by shaking with H_2SO_4) were placed in a 3-l. three-necked flask equipped with a mechanical stirrer, a 1-l. pressure equalizing addition funnel, and a Claisen adapter containing a thermometer and a drying tube. 1,4-Cyclohexanediol (206.7g, 1.8 mol) was dissolved in the chloroform-pyridine solution to give a clear, pale-yellow solution. A solution of benzoyl chloride (198.4 ml, 1.7 mol) in 500 ml of chloroform was added, with stirring, over a period of six hr, the temperature of the reaction mixture being maintained at 0-5° by external cooling. The resulting clear, orange-brown solution was allowed to remain at room temperature overnight, after which time it was freed from pyridine by extraction with 3-500 ml portions of water followed by 1-700 ml portion of dilute sulfuric acid. The chloroform solution was dried over $MgSO_4$, filtered, and the solvent evaporated. The resulting clear, orange oil was distilled under reduced pressure to yield 150g (47% based on unrecovered diol) of the cis-trans mixture of monobenzoates as a colorless, very viscous oil: bp 173-175° (2 mm) (lit[48] bp 175-178° (0.2 mm)); nmr ($CDCl_3$): δ 1.9 (broad multiplet, 8H, ring CH_2), δ3.13 (singlet, 1H, disappears on shaking with D_2O, OH), δ3.85 (broad, 1H, hydroxyl methine), δ 5.17 (broad, 1H,

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(48) E. R. H. Jones and F. Sondheimer, J. Chem. Soc., 615 (1949).

benzoate methine), δ 7.52 (3H) and δ 8.13 (2H) (multiplets, phenyl-H); ir (liquid film): 3400 (m, OH), 3040 (w, phenyl-H), 2930, 2870 (m, alkyl-H), 1720 (s, ester), 1600, 1580, 1500, 1450 (m, phenyl nucleus), 1070 (s, secondary alcohol), 710, 685 (mono-substituted phenyl).

(2) Preparation of 4-Benzoyloxycyclohexanone[48]

A solution of 1, 4-cyclohexanediol monobenzoate (150g, 0.7 mol) in 250 ml of acetic acid was placed in a 1-l. three-necked flask equipped with a 150 ml pressure equalizing addition funnel, a mechanical stirrer, and a thermometer. A solution of chromium trioxide (65g, 0.6 mol) in 38 ml H_2O and 150 ml acetic acid was added dropwise to the stirred solution over a period of six hr, the temperature of the reaction mixture being kept below 35° by external cooling. The reaction was completed by leaving the solution overnight at room temperature. The resulting blue-green solution was diluted with one l. of ether and washed with 5-500 ml portions of H_2O, 1-400 ml portion of 5% HaOH solution, and finally with 1-500 ml portion of H_2O to give a clear, pale yellow ether layer. The ether layer was dried over $MgSO_4$, filtered and the solvent evaporated to give a white, powdery, sweet-smelling solid. Recrystallization from petroleum ether (bp 30-60°) gave 136.4g (89%) of the keto ester as white, translucent plates: mp 63-63.5° (lit[48] mp 63-64°); nmr ($CDCl_3$): δ2.32 (broad multiplet, 8H, ring CH_2), δ 5.32 (broad multiplet, 1H, benzoate methine), δ 7.35 (3H) and δ 7.90 (2H) (multiplets, phenyl-H).

(3) Preparation of 4-Benzoyloxycycloheptanone[49]

(a) Preparation of 4-Benzoyloxycycloheptanone Semicarbazone

4-Benzoyloxycyclohexanone (20.0g, 0.092 mol), 350 ml of absolute ethanol, and 0.60g (0.0044 mol) of anhydrous K_2CO_3 were added to a 1-l. three-necked flask equipped with a mechanical stirrer, a thermometer, and a claisen adapter containing a 1-l. pressure equalizing addition funnel and a drying tube. A solution of 14.3g (0.108 mol) of N-nitrosomethylurethane in 330 ml of absolute ethanol was added, with stirring, over a period of seven hr, the temperature of the reaction mixture being kept at -6° by external cooling. After warming slowly to room temperature overnight, the resulting yellowish mixture was filtered, treated with a few drops of glacial acetic acid (no color change observed), and concentrated (rotary evaporator) to a final volume of approximately 30 ml. This material was added to a filtered solution of semicarbazide hydrochloride (10.3g, 0.092 mol) and anhydrous sodium acetate (15.5g) in 103 ml of water, with the aid of 25 ml of 95% ethanol to complete the transfer. While this mixture was heating in a 75° water bath, a yellow-white solid formed, which, after being heated for an additional 0.5 hr, was filtered to give 16.5g of crude semicarbazone. Soxhlet extraction of this material with n-hexane for a period of three days yielded 8.0g (35%) of a pale yellow-white solid as unextractable material: mp 178-182° (lit[49] mp 164-168°); nmr ($CDCl_3$): δ 2.2 (broad multiplet, ring

(49) Peter Yates and Charles D. Anderson, Can. J. Chem., 41, 1033 (1963).

CH_2), δ 5.2 (broad, benzoate methine), δ 5.65 (broad, disappears on shaking with D_2O, NH), δ 7.45 and δ 8.05 (multiplets, phenyl-H); ir ($CHCl_3$): 3500, 3400 (w, amide), 3040 (w, phenyl-H), 2930, 2860 (w, alkyl-H), 1720 (s, ester), 1690, 1570 (s, amide), 1580, 1450 (m, phenyl nucleus).

(b) Preparation of 4-Benzyloxycycloheptanone[49]

4-Benzoyloxycycloheptanone semicarbazone (18.9g, 0.066 mol) was placed in a continuous liquid-liquid extractor and dissolved in 125 ml of 10.5N NCl. The resulting clear, pale-yellow solution was continuously extracted with ether over a period of 47 hr. The final ether solution (600 ml) was washed with 70 ml of water, 70 ml of 1N K_2CO_3 solution, and finally 2-100 ml portions of saturated NaCl solution. Drying with $MgSC_4$, filtration, and evaporation of the solvent yielded 10.6g (70%) of a clear, yellowish, viscous oil which solidified on standing. Two recrystallizations from hexane gave white, needle-like crystals: mp 53-54.5° (lit[49] bp 145-149° (10^{-3} mm)); nmr ($CDCl_3$): δ2.0 and δ2.5 (multiplets, 10H, ring CH_2), δ 5.12 (braod, 1H, benzoate methine), δ7.25 and δ7.80 (multiplets, 5H, phenyl-H); ir (liquid film): 3040 (w, phenyl-H), 2950, 2870 (m, alkyl-H), 1710 (s, broad, ketone and ester), 1600, 1580, 1500, 1450 (m, phenyl nucleus), 715, 685 (s, monosubstituted phenyl).

(4) Preparation of 1-Methyl-1,4-cycloheptanediol (LXII)

A solution of methyllithium (5.08% in diethyl ether, 160 ml, 0.26 mol) was placed in a 500-ml three-necked flask equipped with a 125-ml pressure equalizing addition funnel, a mechanical stirrer, and a reflux condenser containing a drying tube. A solution of 4-benzoyloxycycloheptanone (8.36g, 0.036 mol) in 60 ml of anhydrous ether was added dropwise to the stirred solution over a period of six hr. The white suspension which formed was hydrolyzed by the dropwise addition of 100 ml of water to the cooled reaction mixture. The resulting two layers were separated, and the aqueous layer was first saturated with K_2CO_3, and then extracted with 5-100 ml portions of ether. Drying with $MgSO_4$, filtration and evaporation of the solvent gave 8.2g of viscous, yellowish oil. Column chromatography on silica gel yielded two fractions: fraction one, eluent 100% ether, 3.94g (80%) of 2-phenyl-2-propanol, ir identical with that of an authentic sample; fraction two, eluent 15% methanol-ether, 3.52g (70%) of a clear, viscous, nearly colorless oil; nmr ($CDCl_3$): δ 1.20 and 1.22 (sharp singlets, 1:1 ratio, cis-trans methyls), δ 1.62 (broad multiplet, ring CH_2), δ 3.10 (sharp singlet, OH), δ 3.80 (broad, hydroxy methine); ir (liquid film): 3350 (s, OH), 2930, 2870 (s, alkyl-H), 1100 (w, tertiary-OH), 1040 (s, secondary-OH).

(5) Preparation of 1-Methyl-8-oxabicyclo[3.2.1]octane (LXIII)[50]

A solution of 1-methyl-1,4-cycloheptanediol (LXII) (0.51g, 0.0035 mol) in 4 ml of dry pyridine was placed in a 25-ml three-necked flask equipped with a 25-ml pressure equalizing addition funnel, a magnetic stirrer, and a reflux condenser containing a drying tube. A solution of p-toluenesulfonyl chloride (0.86g, 0.0042 mol) in 6.5 ml of dry pyridine was added dropwise to the stirred solution over a period of 20 min, the temperature of the reaction mixture being maintained at 120°. The resulting wine-red solution was allowed to cool, and was then poured onto an ice-sulfuric acid slurry. This material was extracted with 5-20 ml portions of pentane. Drying with $MgSO_4$, filtration, and evaporation of the solvent gave 0.30g (60% yield) of crude product. Purification was effected by preparative gas chromatography (20% DC550 on 60/80 chromosorb P). A clear, colorless liquid with a pungent odor was obtained; ir (liquid film): 2930, 2870 (s, alkyl-H), 1370 (m, methyl), 1040, 1025 (s, ether).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.15; H, 11.26.

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(50) Patterned after A. P. Krapcho and B. P. Mundy, J. Heterocycl. Chem. 2, 355 (1965).

(M) Reactions in Sulfuric Acid

(1) The Reaction of 2, 2-Dimethyl-1, 1, 3, 3-Tetradeuterio-1, 3-propanediol (Xa)

This reaction is representative of those performed on the water soluble alcohols in the series (Table II, p 18). A typical experiment was carried out as follows: A 50% sulfuric acid solution (250 ml) was placed in a 500-ml three-necked flask equipped with a magnetic stirrer, a gas inlet tube with a sintered glass bottom, a 150-ml pressure equalizing addition funnel, and a Claisen distilling head containing an Allihn condenser connected to a series of two 2-l. flasks and three traps immersed in dry ice-acetone baths. A vigorous nitrogen flow was passed through the preheated sulfuric acid solution (160°), and a solution of 2, 2-dimethyl-1, 1, 3, 3-tetradeuterio-1, 3-propanediol (5.0g, 0.05 mol) in 100 ml of water was added at such a rate as to maintain constant acid volume in the reaction flask. After the addition was completed, 50 ml of water were added to the reaction mixture in a similar manner.[51]

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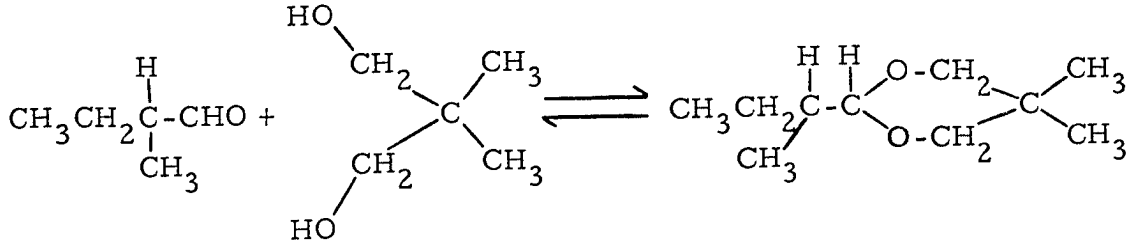
(51) When the reaction was not continued by the addition of water,



XIV X XXI

very little 2-methylbutyraldehyde was observed among the products. This

The distillates collected in the five traps were combined and extracted with 4-100 ml portions of methylene chloride. Drying with $MgSO_4$, filtration, and distillation of the solvent gave a clear, orange oil, which was analyzed by glc (diethylene glycol adipate, 20% on 60/80 mesh chromosorb P, 60 cc of helium per min, 70°). Two peaks were observed, corresponding to 2-methylbutyraldehyde (XIV) (60%) and methyl isopropyl ketone (XX) (40%). The removal of volatile material by distillation (oil bath to 200°) gave a residual clear, red oil whose nmr spectrum was comparable to that of an authentic sample of 5,5-dimethyl-2(2-butyl)-1,3-dioxane (XXI) (a similar residue from unlabeled diol (X) gave ir and nmr spectra identical to those of an authentic sample). Based on starting material, the acetal (XXI), and the aldehyde (XIV) plus ketone (XX) fractions were each obtained in 15% yield.

Preparative gas chromatography of the aldehyde (XIV) plus ketone (XX) fraction gave two colorless liquids which were analyzed by nmr and mass spectrometry.

The nmr and mass spectra of the 2-methylbutyraldehyde (XIV) are discussed on page 13.

The nmr spectrum of the methyl isopropyl ketone (XX) follows: nmr ($CDCl_3$): δ1.10 (sharp doublet, isopr CH_3), δ2.13 (sharp singlet, $COCH_3$) δ2.60 (septet, methine). Integration shows the ratio of isopropyl

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result is consistent with the previously observed stability of the acetal, 5,5-dimethyl-2(2-butyl)-1,3-dioxane (XXI).[14] In this case, longer reaction time evidently shifts the equilibrium to the left as more diol (X) is consumed.

methyl to acetyl methyl to be 1.7 to 1. The mass spectrum of the methyl isopropyl ketone (XX) is discussed on page 13.

(2) The Reaction of 2-Methylbutyraldehyde (XIV)

This reaction is representative of those performed on the water insoluble materials in the series (Table II, p 18). A typical experiment follows: A 50% sulfuric acid solution (300 ml) was placed in a 500-ml three-necked flask equipped with a magnetic stirrer, two gas inlet tubes with sintered glass bottoms, a 150-ml pressure equalizing addition funnel, and a Claisen distilling head containing an Allihn condenser concected to a series of two 2-l. flasks and three traps immersed in dry ice-acetone baths. A vigorous nitrogen flow was passed through the preheated sulfuric acid solution (160°) by way of one gas inlet tube. The second tube was fitted with a side arm containing a septum, and 2-methylbutyraldehyde (XIV) (5.0g, 0.06 mol) was injected in 200 μl portions, with the aid of a second slow stream of nitrogen. Water (a total of 450 ml) was added dropwise through the additional funnel at such a rate as to maintain constant acid volume. The combined distillates were extracted with 5-100 ml portions of methylene chloride. Drying with $MgSO_4$, filtration, and distillation of the solvent gave a clear, yellow oil (3.0g, 60%), which was analyzed by glc (diethylene glycol adipate, 20% on 60/80 mesh chromosorb P, 60 cc of helium per min, 70°). Two peaks were observed, corresponding to 2-methylbutryaldehyde (XIV) (75%) and methyl isopropyl ketone (XX) (25%). Nmr analysis confirmed the presence of aldhyde (XIV) and ketone (XX): nmr (neat): δ0.90 (distorted triplet, terminal CH_3 (ald.)), δ 1.10 (sharp doublet, α-CH_3 (ald.), isopr CH_3 (ket.)), δ1.50 (multiplet, CH_2(ald.)), δ2.10 (sharp singlet, $COCH_3$ (ket.)), δ2.22 (multiplet, methine (ald., ket.)).

(3) The Reaction of 2-Methyl-3-buten-2-ol(XLIV)

A 50% sulfuric acid solution (250 ml) was placed in a 500-ml three-necked flask equipped with a magnetic stirrer, a gas inlet tube with a sintered glass bottom, a 150-ml pressure equalizing addition funnel, and a Claisen distilling head containing an Allihn condenser connected to a series of two 2-l. flasks and three traps immersed in dry ice-acetone baths. A vigorous nitrogen flow was passed through the preheated sulfuric acid solution (158°) and a solution of 2-methyl-3-buten-2-ol (XLIV)(5.0g, 0.06 mol) in 110 ml of water was added at such a rate as to maintain constant acid volume in the reaction flask. The distillates collected in the five traps were combined and extracted with 2-100 ml portions of methylene chloride. Drying with $MgSO_4$, filtration, and distillation of the solvent gave 3.5g (70%) of a clear, orange oil. Glc analysis was able to detect only a trace of methyl isopropyl ketone (XX) and 2-methylbutyraldehyde (XIV). Two other peaks were present (also traces), corresponding to starting material and its allylic isomer, 3-methyl-2-buten-1-ol (XLIII). The bulk of the material was not eluted from the column. Mass spectral analysis revealed the presence of high molecular weight material with the general formula $(C_5H_8)_n$.

Under conditions identical to those described above, except that the starting 2-methyl-3-buten-2-ol (XLIV) solution was diluted 10-fold, the methyl isopropyl ketone (XX) (90%) plus 2-methylbutyraldehyde (XIV) (10%) fraction increased to 7%, and the high molecular weight fraction decreased to 33%.

(4) The Reaction of 3-Methyl-2-buten-1-ol (XLIII)

In a manner similar to that described for the reaction of 2-methyl-3-buten-2-ol (XLIV)(p 106), a solution of 3-methyl-2-buten-1-ol (XLIII)(2.4g, 0.03 mol) in 95 ml of water was added to a 50% sulfuric acid solution. The product composition, as indicated by glc analysis (p 103) was identical to that obtained from 2-methyl-3-buten-2-ol (XLIV).

(5) The Reaction of 3-Methyl-3-buten-1-ol (XXXII) with Deuteriosulfuric Acid

In a manner similar to that described for the reactions in sulfuric acid (p 102), a solution of 3-methyl-3-buten-1-ol (XXXII)(5.6g, 0.07 mol) in 135 ml of D_2O was added to a 45% deuteriosulfuric acid solution. After workup, a clear, brown oil was isolated (1.5g, 30%) which, by glc analysis (p 103) was found to contain only a trace of methyl isopropyl ketone (XX) (90%) and α-methylbutyraldehyde (XIV)(10%). The bulk was composed of high molecular weight material, which mass spectral analysis revealed to be heavily deuterated compounds with the general formula $(C_5H_8)_n$. Similar results were obtained when the acid concentration was reduced to 30%.

However, when the starting 3-methyl-3-buten-1-ol (XXXII) solution was diluted 20-fold, the reaction with 45% deuteriosulfuric acid gave a 17% yield of methyl isopropyl ketone (XX)(90%) and 2-methylbutyraldehyde (XIV)(10%), and only a 15% yield of high molecular weight material.

When 3-methyl-3-buten-1-ol (XXXII)(2.0g, 0.03 mol) was added all at once to a 10% deuteriosulfuric acid solution (80 ml, 118°), and the resulting mixture heated for an additional 8 min, two layers were observed to form in the reaction flask. The flask was immediately immersed in an ice-water bath. The reaction mixture was neutralized with K_2CO_3 and the D_2O was evaporated to give a wet, white solid, which was extracted with 2-50 ml portions of ether. Drying with $MgSO_4$, filtration, and evaporation of the solvent gave 0.09g (5%) of a

clear, viscous, pale-yellow oil. The nmr spectrum proved to be similar to that of 3-methyl-1,3-butanediol (XLVII)(p 116), where differences in peak intensity suggest deuterium incorporation.

(6) The Reaction of 1, 1-Bis-(hydroxydeuteriomethyl)cyclohexane (LXXVIIa)

This reaction is representative of those performed on the diols in the cyclic series (p 51 - p 71). A typical experiment was carried out as follows: A 50% sulfuric acid solution (250 ml) was placed in a 500-ml three-necked flask equipped with a magnetic stirrer, a gas inlet tube with a sintered glass bottom, a 1-l. pressure equalizing addition funnel, and a Claisen distilling head containing an Allihn condenser connected to a series of two 2-l. flasks and three traps immersed in dry ice-acetone baths. A vigorous nitrogen flow was passed through the preheated sulfuric acid solution (162°) and a solution of 1, 1-bis-(hydroxydeuteriomethyl)cyclohexane (LXXVIIa) (9.0g, 0.06 mol) in 1000 ml of water was added at such a rate as to maintain constant acid volume in the reaction flask. The distillates collected in the five traps were combined and extracted with 6-100 ml portions of methylene chloride. Drying with $MgSO_4$, filtration, and evaporation of the solvent from an ice-water bath gave 6.5g (79%) of a clear, red-brown oil, which was analyzed by glc (DC550, 20% on 60/80 mesh chromosorb P, 60 cc of helium per min, 155°). Five major peaks were observed, corresponding to 1-methyl-8-oxabicyclo[3.2.1]octane (LXIII)(31.7%), α-methylcyclohexanecarboxaldehyde (LXXVIII)(15.9%), methyl cyclohexyl ketone (LXXIX)(15.9%), α-methylcycloheptanone (LXXX)(20.2%), and cycloheptanecarboxaldehyde (LXXXI)(16.3%). The relative amount of each component present in the mixture was similar to that observed from the reactions of 1-hydroxymethylcycloheptanol (LXXXII)(p 113).

Preparative gas chromatography of the mixture gave five colorless liquids which were analyzed by nmr spectrometry.

The nmr spectrum of the 1-methyl-8-oxabicyclo [3.2.1] octane (LXIII) follows: nmr (CCl_4): δ1.20 (sharp singlet, CH_3), δ1.60 (multiplet, CH_2), δ4.25 (multiplet, CH). Integration shows that CH_3: CH_2 : CH = 3:10.6:1 (theoretical for unlabeled ether (LXIII); CH_3:CH_2:CH = 3:10:1).

The nmr spectrum of the α-methylcyclohexanecarboxaldehyde (LXXVIII) plus the α-methylcyclohexanecarboxylic acid contaminant (see p 52) follows: nmr (CCl_4): δ0.97 (singlet, CH_3 of aldehyde), δ1.23 (singlet, CH_3 of acid), 1.48 (multiplet, CH_2), δ9.05 (singlet, CHO), δ10.35 (singlet, COOH). Integration of the methyl region shows that approximately 60% of the mixture is acid, and comparison of the aldehyde and methyl regions shows that the aldehyde fraction is at least 20%-CDO.

The nmr spectrum of the methyl cyclohexyl ketone (LXXIX) follows: nmr (CCl_4): δ1.50 (multiplet, CH_2), δ2.03 (sharp singlet, CH_3), δ2.50 (multiplet, CH).

The nmr spectrum of the α-methylcycloheptanone (LXXX) follows: nmr (CCl_4): δ0.96 (sharp doublet, CH_3), δ1.66 (multiplet, CH_2), δ2.40 (multiplet, CH_2CO and CHCO). Integration shows the ratio of ring hydrogen to methyl hydrogen to be 4.5 to 1 (theoretical for unlabeled ketone = 3.67:1).

The nmr spectrum of the cycloheptanecarboxaldehyde (LXXXI) plus the cycloheptanecarboxylic acid contaminant (see p 52) follows:

nmr (CCl_4): δ 1.57 (broad singlet, CH_2 of aldehyde and acid), δ 2.30 (broad multiplet, CH of aldehyde and acid), δ 9.23 (singlet, CHO), δ 10.40 (broad singlet, COOH). Integration shows the ratio of methylene hydrogen to methine hydrogen to be 9.6 to 1 (theoretical for unlabeled aldehyde = 12 to 1).

(7) The Reaction of 1-Hydroxymethylcycloheptanol (LXXXII)

A 35% sulfuric acid solution (500 ml) was placed in a 1-l. three-necked flask equipped with a magnetic stirrer, a gas inlet tube with a sintered glass bottom, a 1-l. pressure equalizing addition funnel, and a Claisen distilling head containing an Allihn condenser connected to a series of two 2-l. flasks and three traps immersed in dry ice-acetone baths. A vigorous nitrogen flow was passed through the preheated sulfuric acid solution (155°), and a solution of 1-hydroxymethylcycloheptanol (4.0g, 0.03 mol) in 400 ml of water was added at such a rate as to maintain constant acid volume in the reaction flask. After the addition was completed 300 ml of water were added to the reaction mixture in a similar manner. The distillates collected in the five traps were combined and extracted with 4-100 ml portions of methylene chloride. Drying with $MgSO_4$, filtration, and evaporation of the solvent from an ice-water bath gave 4.2g of a clear, yellow-green oil, which was analyzed by glc (DC 550, 20% on 60/80 mesh Chromosorb P, 60 cc of helium per min, 150°). Four major peaks were observed, corresponding to 1-methyl-8-oxabicyclo [3.2.1] octane (LXIII)(12.5%), α-methylcyclohexanecarboxaldehyde (LXXVIII)(15.1%), α-methylcycloheptanone (LXXX) (12.7%), and cycloheptanecarboxaldehyde (LXXXI)(59.7%). Methyl cyclohexyl ketone (LXXIX) was essentially absent from the product mixture. The relative amount of each component present in the mixture was similar to that observed from the reaction of 1,1-bis-(hydroxymethyl)cyclohexane (LXXVII) in 35% sulfuric acid. Glc analysis of the products from the reaction in 50% sulfuric acid indicated the

presence of five major peaks, corresponding to 1-methyl-8-oxabicyclo-[3.2.1]octane (LXIII) (31.2%), α-methylcyclohexanecarboxaldehyde (LXXVIII) (12.2%), methyl cyclohexyl ketone (LXXIX)(16.8%), α-methylcycloheptanone (LXXX)(25.0%), and cycloheptanecarboxaldehyde (LXXXI)(14.8%). The relative amount of each component was similar to that observed from the reaction of 1,1-bis-(hydroxymethyl)-cyclohexane (LXXVII) in 45% sulfuric acid and the reaction of 1,1-bis-(hydroxydeuteriomethyl)cyclohexane (LXXVIIa) in 50% sulfuric acid (p 110).

SPECTRA