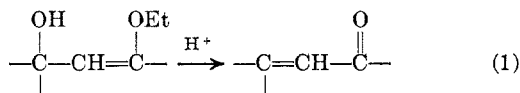# Mechanism of the Acid-Catalyzed Rearrangement of 3-Ethoxy-2-cyclohexenol[1]

MARTIN STILES[2] AND ALLAN L. LONGROY

*Department of Chemistry, University of Michigan, Ann Arbor, Michigan*

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The conversion of 3-ethoxy-2-cyclohexenol (II) to 2-cyclohexenone (III) and ethanol occurs at a convenient rate in the pH range 7–9 at 25°, and the observed first-order rate constant is directly proportional to the hydrogen ion concentration. When the reaction was carried out in ¹⁸O-enriched water, the ethanol produced was of normal isotopic content and the 2-cyclohexenone was enriched in ¹⁸O. The evidence supports a mechanism (eq 3–7) involving rearrangement of II to its allylic isomer, the hemiketal of 2-cyclohexenone.

The smooth conversion of β-alkoxyallylic alcohols to α,β-unsaturated carbonyl compounds (eq 1) was discovered independently by Woods[3] and by Arens and van Dorp.[4] The development of straightforward methods for the preparation of the alkoxyallylic alcohols has resulted in rather wide application of this reaction in preparative work. The convenient synthesis of 2-cyclohexenone (III) from dihydroresorcinol (eq 2) provides a good example.[5]

(1)

(2)
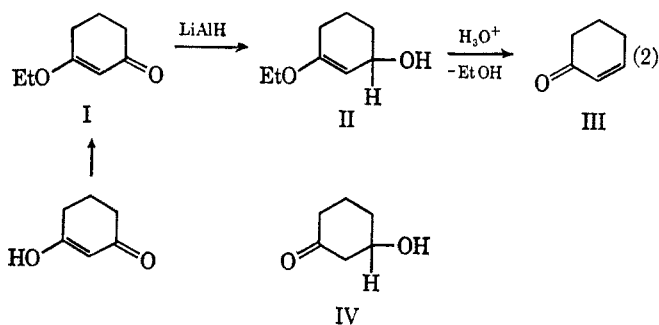
The mechanism of the final step in this scheme has not been determined, although it has been the object of much speculation, most of which has implicated the hydroxy ketone. Data were reported[7] which prove that the hydroxy ketone (IV) is not an intermediate in the conversion of 3-ethoxy-2-cyclohexenol (II) to 2-cyclohexenone (III). This paper presents the results of a study of this acid-catalyzed transformation, using kinetic and isotopic tracer techniques.

Results

The preparation of α,β-unsaturated carbonyl compounds by the method of eq 2 often does not involve isolation of the β-alkoxyallylic alcohol intermediate. However, careful alkaline work-up of the lithium aluminum hydride reduction of the enol ether (I) afforded II, which could be purified by distillation. The com-

pound can be stored in the absence of moisture for several weeks without noticeable decomposition, but treatment with dilute acid converts it rapidly and quantitatively into 2-cyclohexenone. Even shaking with distilled water, in which it is moderately soluble, causes fairly rapid conversion to the ketone.

The rate of the transformation of II to III in dilute, aqueous solution was easily measured spectrometrically at 230 mμ, where the unsaturated ketone has an absorption maximum with ε 1.10 × 10⁴. The reaction followed a first-order rate law with excellent precision under all conditions studied. Figure 1 illustrates the fit of the data obtained in phosphate buffers at three different concentrations of hydrogen ion.

Figure 2 shows a plot of the first-order rate constants as a function of hydrogen ion concentration over the pH range 7–9. A slight deviation of the points from the best straight line passing through the origin may possibly reflect a small contribution to the rate from acids other than hydrogen ion. Such catalysis could not be established with certainty, however. The four experiments summarized in Table I failed to detect

TABLE I
EFFECT OF BUFFER CONCENTRATION UPON THE RATE[a]

10^3[NaH₂PO₄], M	10^3[Na₂HPO₄], M	$10^4 k$, sec⁻¹
3.02	15.65	2.97
1.81	9.39	3.10
1.21	6.26	3.14
0.603	3.13	3.33

[a] The ionic strength was maintained at 0.05 M by addition of sodium chloride.

catalysis by dihydrogen phosphate ion at the concentrations indicated. The 10% increase in rate which was observed as the buffer concentration was *decreased* fivefold was approximately that predicted for the small shift toward neutrality (*ca.* 0.02 pH unit) which accompanied dilution of the buffer. One may conclude that acids other than hydrogen ion make a negligible contribution to the rate under the conditions of our experiments. It is possible that more extensive study of the reaction at lower hydrogen ion concentration would reveal general acid catalysis.

The reaction was allowed to proceed in ¹⁸O-enriched water, and both the ethanol and cyclohexenone produced were examined. The mass spectrum of the ethanol was the same as that of ethanol used to prepare II. The cyclohexenone was pyrolyzed at 600–650° and the carbon monoxide obtained was analyzed in the mass spectrometer. The results presented in Table II show that the oxygen of the ketone is derived from the solvent.

(1) The experimental results in this paper formed a part of the Ph.D. thesis of A. L. Longroy, University of Michigan, 1962.

(2) Fellow of the Alfred P. Sloan Foundation, 1961–1965.

(3) G. F. Woods, *J. Am. Chem. Soc.*, **69**, 2549 (1947); G. F. Woods and I. W. Tucker, *ibid.*, **70**, 2174 (1948).

(4) J. F. Arens and D. A. van Dorp, *Nature*, **160**, 189 (1947); *Rec. Trav. Chim.*, **67**, 973 (1948).

(5) H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953); W. F. Gannon and H. O. House, *Org. Syn.*, **40**, 14 (1960). For other examples of this method, see ref 6 and the papers cited in our preliminary communication.[7]

(6) (a) H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **84**, 4527 (1962); (b) E. Wenkert and D. P. Strike, *ibid.*, **86**, 2044 (1964).

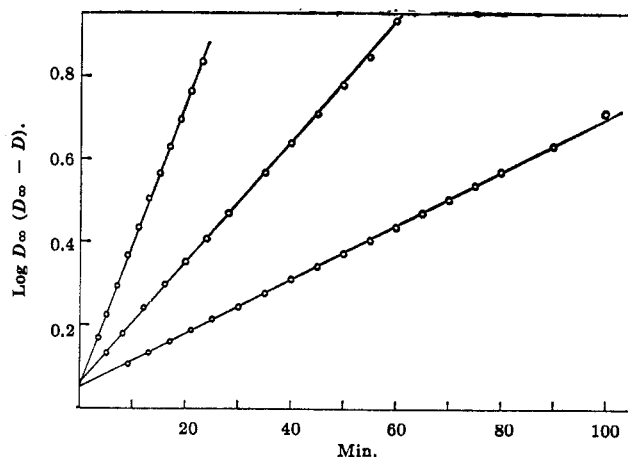(7) M. Stiles and A. L. Longroy, *Tetrahedron Letters*, No. 10, 337 (1961).

Figure 1.—First-order plots for the conversion of 3-ethoxy-2-cyclohexenol (II) to 2-cyclohexenone (III) in phosphate buffer at 25.2°; left to right: pH 7.01, 7.40, 7.79.
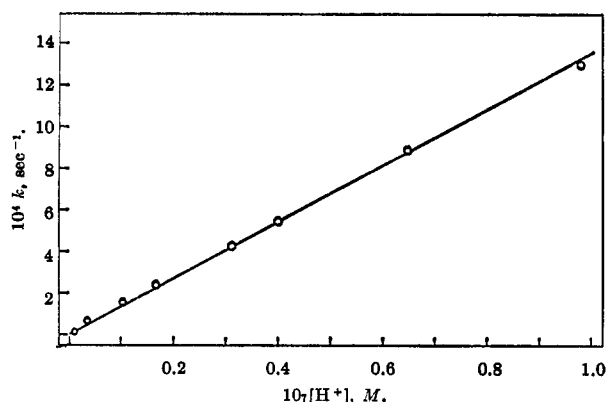

Figure 2.—Dependence of first-order rate constants upon hydrogen ion concentration.

TABLE II

MASS SPECTROMETRIC ANALYSIS OF CARBON MONOXIDE

| Sample	Atom % of ^{18}O
Natural abundance (measured)	0.242
Control	0.270
Reaction	1.29
Calculated[a]	
Case I	1.16
Case II	1.3
Case III	0.27

[a] See the Experimental Section for calculations.

Discussion

Braude[8] included the reaction under discussion in a review of allylic rearrangements, linking it with the rearrangement of β-chlorovinylcarbinols, reported by Jones and Weedon.[9] As we have previously noted,[7] our data are consistent with this view, and the mechanism of eq 3–7 will therefore be used as a basis for discussion.

The possibility that the decomposition of the hemiketal (eq 7) is slow enough to limit the measured process is rendered very unlikely by the kinetic data. The formation and decomposition of hemiacetals, such as glucose[10] and the hemiacetal of acetaldehyde,[11] as

(8) E. A. Braude, Quart. Rev. (London), 4, 407 (1950).

(9) E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 937 (1946).

(10) J. N. Brønsted and E. A. Guggenheim, J. Am. Chem. Soc., 49, 2554 (1927).

(11) G. W. Meadows and B. de B. Darwent, Trans. Faraday Soc., 48, 1015 (1952).

well as of acetaldehyde hydrate,[12] exhibit general catalysis by acids and bases, the latter being generally more efficient. In the present case neither bases nor undissociated acids make a measurable contribution to the reaction rate. Furthermore, the decomposition of hemiacetals is very fast at 25°[11,12] when the acetal link is noncyclic. It is concluded, therefore, that the measured process is the conversion of V to VI.
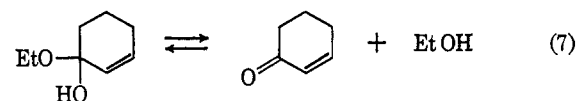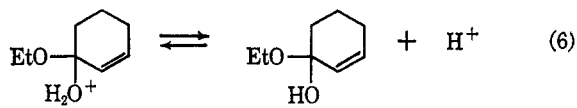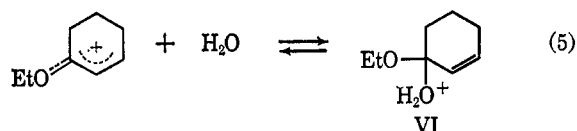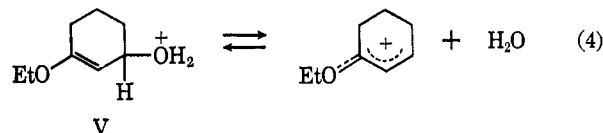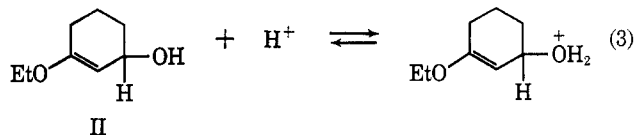
The hydrolysis in ^{18}O-enriched water furnished evidence in favor of the proposed mechanism. An alternative to eq 5, such as a displacement reaction involving rupture of the Et–O bond (eq 8), was readily eliminated when it was found that the ethanol produced was not enriched in ^{18}O.
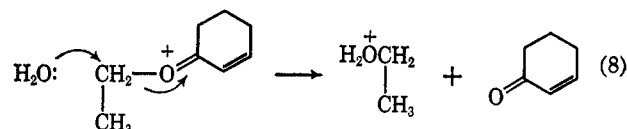
It is clear from the data that the ketone oxygen is derived from the solvent water. The degree of ^{18}O enrichment (1.29 atom %) is necessarily less than that of the water used in the experiment, since the mole ratio of solvent to substrate was small enough ($\sim$4) that the labeled water was considerably diluted by the ordinary water formed in the decomposition of the substrate. The level of ^{18}O in the product to be expected from the proposed mechanism can be calculated from two different limiting assumptions. If $k_{-4} \gg k_5$ (case I) then ^{18}O mixing between substrate and solvent would occur faster than the over-all reaction and the expected ^{18}O content of the product would be simply the average of all labile oxygens (1.16 atom %). If, on the other hand, $k_5 \gg k_{-4}$ (case II), the expected ^{18}O content of the product can be calculated by the method outlined in the Experimental Section. This calculation, applied to the experiment described in Table II, yields the figure 1.3 atom %. This number is less accurately calculable than the former owing to the fact that it is obtained by subtracting the gram-

(12) R. P. Ball and W. C. E. Higginson, Proc. Roy. Soc. (London), A197, 141 (1949).

atoms of ^{18}O present initially from those which remain in the water at the end of the reaction, both numbers being relatively large compared to the difference. The data suggest that case II is closer to the experimental figure,[13] but the precision of the data is unfortunately not sufficient to permit a firm decision on this point. One can say only that the labeling data are compatible with the over-all mechanism, regardless of the relative magnitudes of k_{-4} and k_5. More accurate measurements, preferably carried out with nearly equal quantities of substrate and labeled water, would permit one to distinguish between these two kinetic situations. It should furthermore be recognized that none of the kinetic or labeling data can be used to distinguish between case II and an S_N2' reaction between water and protonated substrate. The former representation, involving the highly stabilized alkoxyallylic cation, appears more consistent with the striking reactivity of II, compared with simple allylic alcohols.

In certain cases allylic alcohols have been found to undergo "intramolecular" acid-catalyzed rearrangement.[14] In such cases the water molecule formed by the heterolysis of the protonated alcohol recombines at the γ position more rapidly than it mixes with solvent water. This mechanism (case III) could not be detected in the present case. Operation of the "intramolecular" path would lower the ^{18}O content of the product below that calculated for cases I and II. It seems reasonable to conclude that the greater stability of the alkoxyallylic cation, compared to simple allylic cations, is associated with a longer lifetime of the intermediate, permitting equilibration between water molecules solvating the cation and those comprising the bulk solvent.

As we have previously shown, the corresponding hydroxy ketone (IV) is stable to the mildly acidic conditions under which cyclohexenone is formed rapidly and quantitatively from the alkoxyallylic alcohol (II). It is therefore clear that the rearrangement outlined in eq 3–5 is favored over the alternative process represented by eq 9.

$$\text{(9)}$$

II　　　　　　IV
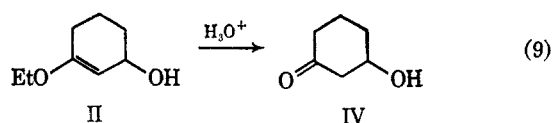
A recent paper by Wenkert and Strike[6b] indicates, however, that the latter process can compete effectively with the former in certain cases. Treatment of the hydroxy enol ether (VII) with mild, aqueous acid led to rapid formation of the corresponding unsaturated ketone, as would have been predicted from the behavior of the simple cyclohexane derivative. By contrast the isomeric hydroxy enol ether (VIII) underwent
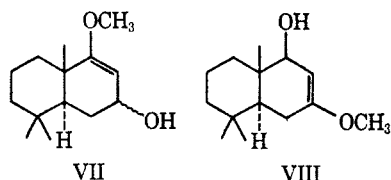
VII　　　　　　VIII

slower conversion to a mixture of unsaturated ketone and the corresponding hydroxy ketone. Evidently the competition between allylic rearrangement and hydrolysis of the enol ether function may be decided by stereochemical features, such as the geometric relationship between the double bond and the alcohol group.[6b] In acyclic or flexible cyclic molecules the geometry which favors the heterolysis of the alcohol function can presumably be readily attained, and the "rearrangement" path is favored by a substantial margin. The two reactions are rather delicately balanced in those rigid molecules possessing a geometry unfavorable for participation of the double bond in the heterolysis of the alcohol group.

Experimental Section

3-Ethoxy-2-cyclohexenone (I) was prepared by the method of Cronyn and Goodrich[15] in 73% yield: bp 133–134° (20 mm), n^{26}D 1.5022 [lit.[15] bp 76° (1 mm), n^{23}D 1.5030].

3-Ethoxy-2-cyclohexenol (II).—3-Ethoxy-2-cyclohexenone (I) (28 g, 0.20 mole) was added to an ether solution of 2.5 g (0.068 mole) of lithium aluminum hydride at such a rate as to maintain gentle reflux. After a further 30 min at reflux the mixture was cooled and hydrolyzed by the addition of 5 ml of water followed by 4.5 ml of 10% aqueous sodium hydroxide. The resulting suspension was stirred for 2 hr, filtered, and dried. Distillation yielded 22.4 g (79%) of colorless liquid, bp 65–66° (0.6 mm). The analytical sample [bp 69° (0.7 mm), n^{25}D 1.4843] was used for the kinetic measurements.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.33; H, 9.84.

Kinetic Measurements.—A sample of 3-ethoxy-2-cyclohexenol (II) was accurately weighed into a 100-ml volumetric flask. The flask was filled to the mark with the appropriate buffer solution, previously brought to the desired temperature, and an aliquot of the mixed solution was quickly diluted tenfold with more buffer. A portion of the diluted solution was placed in the thermostated (25.2 ± 0.1°) cell compartment of a Beckman D.U. spectrophotometer, and the optical density (D) at 230 mμ was measured against pure buffer as the blank. The infinity absorption (D_∞) was observed after more than 10 half-lives, and corresponded satisfactorily in each case to that calculated from the weight of starting material. The observed first-order rate constants were obtained graphically. Figure 1 presents sample plots of the data; the rate constants are collected in Table III. Because the alkoxyallyl alcohol (II) absorbs appreciably at 230 mμ, the plots in Figure 1 do not intersect the ordinate at 0, but at the value log $[\epsilon/(\epsilon - \epsilon')]$ where ϵ and ϵ' are the molar extinction coefficients of the unsaturated ketone (III) and the starting material (II), respectively.

TABLE III

RATE CONSTANTS FOR FORMATION OF 2-CYCLOHEXENONE (III)
FROM 3-ETHOXY-2-CYCLOHEXENOL (II) IN
AQUEOUS BUFFERS AT 25.2°[a]

$10^4[II]_0$	10^3 [NaH$_2$PO$_4$]	10^3 [Na$_2$HPO$_4$]	pH[b]	$10^4 k$ sec^{-1}
2.24	13.9	27.8	7.01	13.1
2.24	9.30	30.2	7.19	8.98
1.95	6.03	31.3	7.40	5.50
2.01	4.55	31.9	7.51	4.30
1.83	2.50	32.5	7.79	2.47
1.68	1.58	32.8	8.00	1.53
1.83	0.508	33.2	8.50	0.570
1.64	NH$_3$–NH$_4$Cl Buffer[c]		9.03	0.144

[a] Ionic strength kept at 0.20 M with NaCl except as noted.
[b] Measured with a glass electrode. [c] Ionic strength 0.18 M.

^{18}O Experiments. A. Examination of Cyclohexenone.—A mixture of 0.7083 g (4.98 mmoles) of 3-ethoxy-2-cyclohexenol

(13) A tendency for unsymmetrical allyl cations to combine with nucleophiles more rapidly at the more substituted position is often observed; see R. H. DeWolfe and W. G. Young, *Chem. Rev.*, **56**, 753 (1956).

(14) H. L. Goering and R. R. Josephson, *J. Am. Chem. Soc.*, **84**, 2779 (1962).

(15) M. W. Cronyn and J. E. Goodrich, *ibid.*, **74**, 3331 (1952).

(II) and 0.3462 g (19.16 mmoles) of ^{18}O-enriched water (1.40 atom % ^{18}O) was shaken until the mixture was homogeneous and then allowed to stand at room temperature for 190 min. The solution was taken up in ethyl ether and passed through a column of Linde Type 3-A Molecular Sieve (predried at 500°F) to remove water and ethanol. Removal of ether and evaporative distillation [ca. 50° (8 mm)] provided the sample of 2-cyclohexenone, which was shown by gas chromatographic analysis to contain 2.3 ± 0.4% unreacted II, indicating that the reaction had proceeded to 98% completion. A 17-mg sample of the unsaturated ketone was pyrolyzed at 600–650° in an evacuated Vycor tube, and the carbon monoxide was analyzed mass spectrometrically. A mixture of 0.5202 g (5.42 mmoles) of 2-cyclohexenone and 0.3485 g (19.4 mmoles) of ^{18}O-enriched water was subjected to identical treatment as a "control" experiment. A sample of pure 2-cyclohexenone was also pyrolyzed to provide carbon monoxide of "normal abundance." The atom per cent of ^{18}O of each sample was determined from the ratio of the peaks at m/e 28 and 30. The results are in Table II.

B. Examination of Ethanol.—A mixture of 0.7026 g (4.95 mmoles) of 3-ethoxy-2-cyclohexenol (II) and 0.3750 g (20.8 mmoles) of ^{18}O-enriched water was allowed to react as described under A. The ethanol produced was separated from water and cyclohexenone by gas chromatography using a 7.5 ft × $^3/_8$ in. column of triethylene glycol on 30–60 Chromosorb P (30 g of absorbent/100 g of support) at 110°. The ethanol was collected from the chromatogram and analyzed directly in the mass spectrometer. A "control" sample was prepared by treating 0.4656 g (10.1 mmoles) of ethanol and 0.7174 g (39.9 mmoles) of ^{18}O-enriched water under the same conditions. A sample of II was hydrolyzed in ordinary water to give the ethanol which served to indicate "normal" ^{18}O content. The mass spectrum of the three samples was the same within the experimental error, as the following relative intensities show (m/e (31) = 100) (see Table IV).
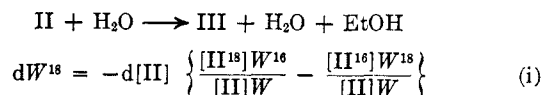
TABLE IV

m/e	Normal	Control	Reaction
46	15.9	15.9	15.9
47	0.52	0.49	0.49
48	0.048	0.048	0.044

Calculations.—The hydrolysis of the alkoxyallylic alcohol in a quantity of ^{18}O-enriched water, sufficient to maintain essentially a constant level of ^{18}O enrichment in the solvent reservoir,

would produce cyclohexenone containing this same level of enrichment, since the ketonic oxygen is derived from the water. In the experiments reported here, however, the substrate and the labeled water were taken in comparable amounts, so that the ^{18}O content of the water changed during the reaction, being diluted by oxygen from the substrate. In order to calculate the ^{18}O content to be expected in the cyclohenone product one has to differentiate between two kinetic situations in the mechanism of eq 3–7. If $k_{-4} \gg k_5$ (case I) mixing will occur between the alcohol oxygen of the substrate and water prior to the formation of product. The ^{18}O content of the cyclohexenone would then be simply the average of all the labile oxygens. If, on the other hand $k_5 \gg k_{-4}$ (case II), the ^{18}O content of the cyclohexenone (and of the water) would change continuously as the reaction proceeds. The level of ^{18}O labeling in the product can be predicted on the basis of eq iii derived below.[16] It is clear that an intermediate kinetic situation ($k_{-4} \sim k_5$) would lead to values intermediate between those calculated for case I and case II.

For the reaction

$$\text{II} + \text{H}_2\text{O} \longrightarrow \text{III} + \text{H}_2\text{O} + \text{EtOH}$$

$$d W^{18} = -d[\text{II}] \left\{ \frac{[\text{II}^{18}] W^{16}}{[\text{II}] W} - \frac{[\text{II}^{16}] W^{18}}{[\text{II}] W} \right\} \tag{i}$$

where W^{18} refers to $[\text{H}_2{}^{18}\text{O}]$, W to total water, etc. Let $\alpha = W^{18}/W$ (a variable), $\beta = [\text{II}^{18}]/[\text{II}]$ (a constant, neglecting kinetic isotope effects), and x = a reaction variable, so that $-d[\text{II}] = [\text{II}]_0 dx$. Then

$$\frac{d\alpha}{\beta - \alpha} = \frac{[\text{II}]_0}{W} dx \tag{ii}$$

Integration of eq ii gives

$$\alpha = \beta + (\alpha_0 - \beta)e^{-[\text{II}]_0 x/W} \tag{iii}$$

Experimentally, $[\text{II}]_0 = 4.98$, $W = 19.16$, $\alpha_0 = 0.0140$, $\beta = 0.00242$, $x = 0.977$, whence $\alpha = 0.0114$ after 97.7% reaction. From the stoichiometry one calculates a corresponding value of 1.3 atom % for the cyclohexenone.

Registry No.—II, 7650-73-9; carbon monoxide, 630-08-0; I, 5323-87-5; III, 930-68-7.

Acknowledgment.—We are indebted to Mr. Frank Drogosz for operation of the mass spectrometer.

The Effect of Manganese on the Chromic Acid Oxidation of Secondary–Tertiary Vicinal Glycols

B. H. WALKER

The Chemical Process Research and Development Division, The Upjohn Company, Kalamazoo, Michigan 49001

The chromic acid oxidation of the two steroidal secondary–tertiary vicinal glycols, "triol acetate" (1, 11β,17α,-20α,21-tetrahydroxy-4-pregnen-3-one 21-acetate) and "Δ^1-triol acetate" (2, 11β,17α,20α,21-tetrahydroxy-1,4-pregnadien-3-one 21-acetate), with or without added manganous ions, has been examined. In the absence of added manganous ions, glycol cleavage is the dominant reaction giving adrenosterone (androst-4-ene-3,11,17-trione, 11) and Δ^1-adrenosterone (androsta-1,4-diene-3,11,17-trione, 12), respectively. In the presence of manganous salts, oxidation of the secondary alcohol to ketone predominates over the cleavage reaction and cortisone acetate (9) and prednisone acetate (10) result. Some consideration is given to the mechanism of the reaction, the stereochemistry of the starting materials, and to the location of the acetate groups.

During the past 15 years a large number of papers have appeared which deal with the mechanism of chromic acid oxidation of alcohols.[1] Major contributions were made by Westheimer and his coworkers[2] who postulate the following scheme: R_2-

$\text{CHOH} + \text{Cr}^{6+} \rightarrow \text{R}_2\text{C}{=}\text{O} + \text{Cr}^{4+}$. In the initial step chromium(VI) is reduced by alcohol to chromium-(IV). Chromium(IV) is an unstable state of chromium and in the presence of chromium(VI) decomposes as follows: $\text{Cr}^{4+} + \text{Cr}^{6+} \xrightarrow{\text{fast}} 2\text{Cr}^{5+}$. Chromium(V) is also unstable and rapidly reacts with alcohols to give

(1) For recent reviews, see (a) R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1964, p 33; (b) K. B. Wiberg, "Oxidation in Organic Chemistry," Academic Press Inc., New York, N. Y., 1965, p 69.

(2) J. J. Cawley and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 1771 (1963), and earlier papers.