[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

The Mechanism of Aldehyde and Primary Alcohol Oxidation[1]

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The oxidation of primary alcohols with chromic acid generally leads to the formation of appreciable amounts of ester which may be explained in three ways: direct esterification of alcohol with the acid formed from it by oxidation, hemiacetal formation and subsequent oxidation to ester, or oxocarbonium ion formed by oxidation of aldehyde and the attack of this on alcohol. Stable cyclic hemiacetals have been oxidized and the relative rates of oxidation of a variety of substances pertinent to this problem have been determined. The hemiacetals show rates much faster than aldehyde or alcohols; in addition, a mixture of aldehyde and alcohol oxidizes much faster than either alone and approaches the speed of the hemiacetals. These facts argue strongly for the hemiacetal as the precursor of ester. On the other hand, excellent evidence has been found for the formation of oxocarbonium ions in the oxidation of aldehydes in the absence of alcohols where hemiacetals formation is not possible.

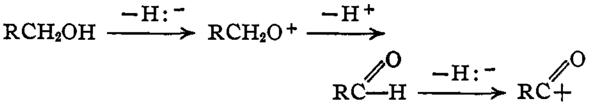
The formation of esters in the oxidation of primary alcohols with chromic acid mixtures is a common experience to all preparative organic chemists and in certain cases forms an excellent method of ester preparation.[2] An early attempt to explain this reaction was made by Milas[3] who oxidized primary alcohols with chlorate in the presence of small amounts of vanadium pentoxide in dilute acid solution and proposed the intermediate formation of hemiacetal and its subsequent oxidation to ester. The Milas mechanism involves the steps

$$\begin{tikzcd}
\text{Primary alcohol} \arrow[r, "\text{Oxid.}"] & \text{Aldehyde} \arrow[d, shift right] & \\
\text{Acetal} \arrow[r, shift left] & \text{Hemiacetal} \arrow[l, shift left] \arrow[u, shift right, "H^+"'] \arrow[r, "\text{Oxid.}"] & \text{Ester}
\end{tikzcd}$$

The only evidence presented by Milas for the hemiacetal mechanism was the fact that the oxidation of acetal under the same conditions led to corresponding amounts of ester. Actually, the acetal will dissolve completely in an acid solution of the strength used by Milas and regenerates alcohol and aldehyde so that this mechanism is based entirely on logical speculation, and Milas has called attention to this fact.[3] On the other hand, the extreme ease of hydrolysis of the simple hemiacetals made us, at first, very skeptical of their formation as intermediates in the oxidation process even though their secondary alcohol nature should make them easily oxidizable. The hemiacetal mechanism has also been advanced by Schulz,[4] who obtained a yield of 90% benzyl trichloroacetate by the chromic acid oxidation of a mixture of chloral and benzyl alcohol. Schulz argued in favor of the hemiacetal mechanism because he obtained little or no ester from those mixtures of aldehyde and alcohol which showed little tendency toward acetal formation. However, the evidence is far from conclusive.

Recently Farkas, *et al.*,[5] have proposed the hemiacetal mechanism for the oxidation of ethyl alcohol to ethyl acetate with free bromine in the presence of bromate. Excellent kinetic data are presented, but the data in no way constitute proof of the hemiacetal mechanism.

Our introduction to this field came from the consideration of the oxidation of aldehydes in an extention of work in this Laboratory on the oxidation of secondary alcohols to ketones with or without accompanying cleavage of the molecule.[6] It appeared a logical extension of this work to assume that



$$RCH_2OH \xrightarrow{-H:^-} RCH_2O^+ \xrightarrow{-H^+} R\overset{O}{\overset{/\!/}{C}}{-}H \xrightarrow{-H:^-} R\overset{O}{\overset{/\!/}{C}}+$$

The oxycarbonium ion $R\overset{O}{\overset{/\!/}{C}}+$, as has been so beautifully established by Newman and his students,[7] should react with water to form acid or with alcohol to form ester. In addition to this mechanism and the hemiacetal formulation, the direct esterification of alcohol with acid formed through oxidation of aldehyde must also be considered, although this latter process could hardly account for high yields of ester under acid conditions. We first sought to eliminate direct acid-catalyzed esterification by the oxidation of a mixture of ethanol and 2,4,6-trimethylbenzaldehyde on the assumption that the acid corresponding to this aldehyde would not undergo simple esterification due to steric hindrance. Unfortunately, chromic acid oxidized the ethyl alcohol, or other primary alcohols tried, faster than the aldehyde, and no significant results could be obtained.[8] The solution to this problem was found in a very simple experiment, however; Moore[9] observed that the oxidation of *n*-butyl alcohol in 70% acetic acid gave about 60% *n*-butyl *n*-butyrate but no *n*-butyl acetate could be detected. Had simple esterification been involved, the acetate should have been present in substantial quantity. The simple esterification of a mixture of *n*-butyl alcohol in a mixture of acetic acid–butyric acid yielded 64% of the acetate and only 4% of the butyrate.[9] Robertson[2] has suggested the direct esterification as the explanation for ester formation, but this mechanism would now appear to be highly improbable.

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[1] Presented in part before the Division of Organic Chemistry, American Chemical Society, Los Angeles, March 19, 1953.

[2] Gilman and Blatt, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 138.

[3] N. A. Milas, THIS JOURNAL, **50**, 493 (1928).

[4] L. Schulz, *Ann. Rept. Essent. Oils, Synthetic Perfumes, Inc., Schimmel & Co.*, 119 (1938).

[5] L. Farkas, B. Perlmutter and O. Schachter, THIS JOURNAL, **71**, 2827 (1949).

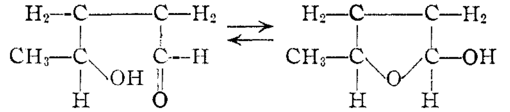
[6] See W. A. Mosher and E. O. Langerak, *ibid.*, **73**, 1302 (1949), for leading references.

[7] M. L. Newman, *et al.*, *ibid.*, **67**, 705 (1945).

[8] L. Wright, Ph.D. Dissertation, Univ. of Delaware, Sept., 1951.

[9] G. L. Moore, Ph.D. Dissertation, Univ. of Delaware, June, 1951.

We felt that it was necessary to have data on the oxidation of relatively stable substances of the hemiacetal type, and the simplest compound to fulfill this requirement appeared to be 2-hydroxy-5-methyltetrahydrofuran (the cyclic hemiacetal related to γ-hydroxy-*n*-valeraldehyde). This substance was first described by Helferich[10] as existing in the cyclic form II on the basis of molecular refraction studies, but it was later shown by Herold[11] to be a ring-chain tautomeric equilibrium of I and II with the equilibrium favoring the cyclic structure



I II

The oxidation of this substance in 70% acetic acid with chromic acid yielded 70% γ-*n*-valerolactone; there was no evidence of the formation of either levulinic acid or levulinic aldehyde. Two explanations may be advanced for the formation of the lactone: (1) the simplest involves direct oxidation of the cyclic hemiactal to lactone or (2) the oxidation of the open form I to give γ-hydroxyvaleric acid which would be readily converted to the corresponding lactone in the acid solution at room temperature. The answer to this question is offered by a simple comparative rate study presented in Fig. 1. Curve A represents the relative rate of oxidation of isovaleraldehyde, curve D 2-pentanol, and curve E 2-hydroxy-5-methyltetrahydrofuran. Had the aldehyde function in the open form oxidized to the corresponding acid, the rate should have been about the same as an aldehyde with the same number of carbon atoms. This is clearly not the case, the rate of the hemiacetal being much faster than that of the aldehyde. Since 2-pentanol also oxidized faster than the aldehyde, a reasonable amount of levulinic aldehyde or acid would have been expected had the reaction proceeded through the open chain form I.

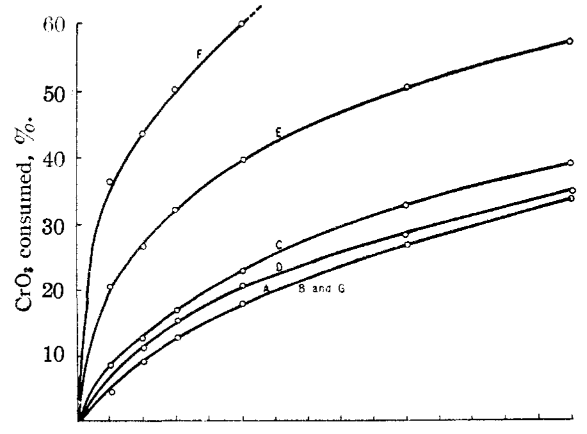


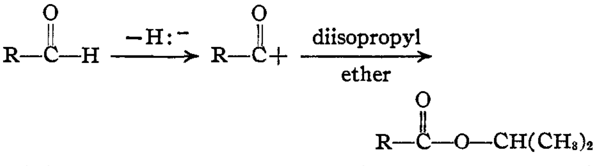
Fig. 1.—CrO_3 oxidation rate study: A, isovaleraldehyde; B, isobutyl alcohol; C, isovaleraldehyde–isobutyl alcohol; D, 2-pentanol; E, 2-hydroxy-5-methyltetrahydrofuran; F, 2-hydroxy-5-methyl-*t*-butyltetrahydrofuran; G, isovaleraldehyde–diisopropyl ether.

2-Hydroxy-5-methyl-5-*t*-butyltetrahydrofuran was also prepared and oxidized with chromic anhydride in acetic acid to yield over 90% of the lactone of 4-hydroxy-4,5,5-trimethylcaproic acid. The rate of the oxidation of this hemiacetal was much greater than the rate of oxidation of 2-hydroxy-5-methyltetrahydrofuran. The *t*-butyl compound would contain a tertiary hydroxyl group in the open chain form, which would only be oxidized with difficulty so that its rapid oxidation is another significant argument for the oxidation of the hemiacetal form. The greater rate over that of the methyl compound is due probably to a greater percentage in the hemiacetal form as a result of stabilization of the ring form by the greater substitution as is the case with the γ-lactones.

Even more convincing, perhaps, is the fact that a mixture of equivalent amounts of isovaleraldehyde and isobutyl alcohol, curve C, oxidizes much faster than the aldehyde or alcohol alone (curves A and B, respectively). Some combination between alcohol and aldehyde, presumably the hemiacetal, must be involved in the acceleration of the oxidation rate.

The fact that aldehyde and corresponding primary alcohol oxidize at about the same rate may appear a bit surprising at first, but, based on our work with 2,4,6-trimethylbenzaldehyde,[9] it was not unexpected. The common belief that aldehydes oxidize easily comes primarily from their ease of autoxidation and not from any great ease of oxidation with acidic agents such as chromic acid. The distinct difference in the rate of autoxidation of aldehydes and the rate with chromic acid is another strong argument against a free radical mechanism for chromic oxidations.

Powerful evidence for the formation of oxocarbonium ions in the oxidation of aldehydes has, however, been found in the absence of alcohol where hemiacetal formation is not possible. A mixture of isovaleraldehyde (0.5 mol) and diisopropyl ether (1 mol) was oxidized in acetic acid solution with chromic anhydride; the products were 59% isovaleric acid and 19% isopropyl isovalerate. The oxidation of a mixture of propionaldehyde, isobutyl alcohol, and diisopropyl ether under similar conditions yielded no isopropyl ester; the products were isobutyl isobutyrate (36%) and isobutyl propionate (34%). In the absence of alcohol, apparently the slower reaction leading to the oxocarbonium may take place as



$$R-\overset{O}{\overset{\|}{C}}-H \xrightarrow{-H:^-} R-\overset{O}{\overset{\|}{C}}+ \xrightarrow[\text{ether}]{\text{diisopropyl}} R-\overset{O}{\overset{\|}{C}}-O-CH(CH_3)_2$$

while in the presence of alcohol the more rapid oxidation of the hemiacetal is favored.

Experimental

Preparation and Oxidation of 2-Hydroxy-5-methyltetrahydrofuran.—In its essential parts, the method of Helferich[10] was followed. Allylacetone, prepared *via* the aceto-

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[10] B. Helferich, *Ber.*, **52**, 1804 (1919).

[11] W. Herold, *Z. physik. Chem.*, **B18**, 165 (1931).

acetic ester method, was reduced to 1-hexene-5-ol with aluminum isopropoxide, ozonized and the ozonide reduced with zinc and acetic acid. The product had the following properties: b.p. 65–67° (10 mm.), n^{25}D 1.43295, *p*-bromophenylhydrazone m.p. 86–88°. *Anal.* Calcd. for $C_5H_{10}O_2$: C, 58.5; H, 9.8. Found: C, 58.68; H, 9.72.

The cyclic hemiacetal, 30 g. in 100 ml. of water, was oxidized with 20 g. of chromium trioxide dissolved in 30 ml. of water. The temperature rose to 70° but subsided within an hour after which the mixture was heated on the steam-bath for two hours. The reaction mixture was continuously extracted with ether, the ether extract dried over sodium sulfate, and distilled. The fraction boiling at 85–87° was identified as γ-*n*-valerolactone, n^{20}D 1.4320, phenylhydrazide m.p. 77–79°, yield 75%. Similar results were obtained when acetic acid was used as solvent in the oxidation.

Preparation and Oxidation of 2-Hydroxy-5-methyl-5-*t*-butyltetrahydrofuran.—Allylacetone (200 g., 2.7 mols) in 500 ml. of ether was added over a 24-hour period to the Grignard reagent prepared from 3.5 moles of *t*-butyl chloride. The product was decomposed with ice and ammonium chloride and worked up in the usual manner. A 22% yield of 5,6,6-trimethyl-1-heptene-5-ol, b.p. 85° (20 mm.), n^{20}D 1.4514, was obtained. This was ozonized and the ozonide decomposed with zinc and acetic acid to yield 79% of 2-hydroxy-5-*t*-butyltetrahydrofuran, b.p. 86° (7 mm.), n^{25}D 1.4535. *Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.35; H, 11.39. Found: C, 68.40; H, 11.76.

Oxidation of 19 g. with 9 g. of chromium trioxide with acetic acid as solvent with ice cooling (temperature under 30°) and isolation as above yielded 18.1 g. (90%) of the lactone of 4-hydroxy-4,5,5-trimethylcaproic acid, n^{20}D 1.4531. *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.23; H, 10.26; sapn. equiv., 156. Found: C, 69.09; H, 10.53; sapn. equiv., 156.2.

Oxidation of Isovaleraldehyde and Isobutyl Alcohol Mixtures.—The two substances, 0.5 mol each, were dissolved in 75 ml. of 80% acetic acid, the mixture cooled to 0° with ice–salt mixture and a solution of 35 g. of chromium trioxide in 250 ml. of 80% acetic acid added over a period of 24 hours with stirring. Water was added, the mixture extracted with ether, the extracts washed with sodium carbonate solution until neutral, the product dried and fractionated through a column of 20 theoretical plates. The following fractions were obtained: (A) b.p. 60–80°, n^{20}D 1.3799, weight 2.5 g., yield 4.2%, identified as isobutyraldehyde, 2,4-dinitrophenylhydrazone m.p. and mixed m.p. 180°; (B) 88–100°, 1.3930, 10.5 g., 24.4%, recovered isovaleraldehyde, 2,4-dinitrophenylhydrazone m.p. and mixed m.p. 122°; (C) 100–115°, 1.3988, 9.6 g. 26%, recovered isobutyl alcohol, 3,5-dinitrobenzoate m.p. and mixed m.p. 85°; (D) 136–150°, 1.4010, 6.6 g., 9%, identified as isobutyl isobutyrate by the method of Hardy[12] to give isobutyrylanilide, m.p. and mixed m.p. 103–104°; hydrolysis with potassium hydroxide in diethyleneglycol gave isobutyl alcohol, m.p. and mixed m.p. of 3,5-dinitrobenzoate 84°; (E) 160–170°, 1.4060, 18.83 g., 23.6%, identified as above as isobutyl isovalerate, anilide of acid fraction m.p. and mixed m.p. 110°, 3,5-dinitrobenzoate of alcohol fraction 84°. From the alkaline washings of the ether extract was obtained a 16.6% recovery of isovaleric acid, anilide m.p. and mixed m.p. 109–110°.

Oxidation of Isovaleraldehyde in the Presence of Diisopropyl Ether.—Isovaleraldehyde (0.5 mol) and diisopropyl ether (1.0 mol) were dissolved in 125 ml. of glacial acetic acid and cooled to 0–5°. To this solution was added over a period of 12 hours 35 g. of chromium trioxide in 10 ml. of water and 200 ml. of acetic acid. When worked up as in the above reactions, 19.4% isopropyl isovalerate, anilide of acid portion m.p. and mixed m.p. 110°, 3,5-dinitrobenzoate of alcohol fraction m.p. and mixed m.p. 121–122°, was obtained. A 59% yield of isovaleric acid was isolated, anilide m.p. and mixed m.p. 110°. No isopropyl acetate was found.

Oxidation of Propionaldehyde in the Presence of Diisopropyl Ether and Isobutyl Alcohol.—The three substances to be oxidized were used in 1-mol amounts and oxidized as in the above experiment. A 34% yield of isobutyl propionate, a 6% of isobutyl isobutyrate and a 14% yield of propionic acid were obtained.

Oxidation Rate Studies.—The general procedure was as follows: 125 ml. of 0.0210 *M* chromium trioxide solution was placed in a 250-ml. flask with ground-glass stopper. The flask was clamped in an ice–water-bath (0°) and the contents agitated with a magnetic stirrer. The substance to be oxidized was weighed from a Lunge pipet and diluted with 85% acetic acid. When temperature equilibrium was reached the substance solution was added quickly to the oxidant solution. The total volume was 150 ml. At intervals, 5-ml. portions were withdrawn, quenched in excess potassium iodide solution and the liberated iodine titrated with thiosulfate in the usual manner. The results are summarized in Fig. 1.

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[12] D. V. N. Hardy, *J. Chem. Soc.*, 398 (1936).

NEWARK, DELAWARE

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE GEORGIA INSTITUTE OF TECHNOLOGY]

The Dehydration of Alcohols in the Presence of Haloforms and Alkali[1]

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It is shown that the ethylene arising from the reaction of haloforms with ethanol and alkali is formed from the ethanol, since the analogous reaction of isopropyl alcohol yields propylene. Olefin is also found in the corresponding reactions of *n*-propanol, all of the butanols and *t*-amyl alcohol. The olefin formed from the latter alcohol is shown to be about 80% 2-methyl-1-butene. Bromoform yields about 30% more olefin from isopropyl alcohol than does either chloroform or bromodichloromethane.

In 1855 Hermann reported that the reaction of bromoform with potassium hydroxide in aqueous ethanol yielded a mixture of carbon monoxide and ethylene containing 25–29% of the latter.[2] The gas produced by the reaction of sodium ethoxide with chloroform was reported by Bassett to consist largely of carbon monoxide, but a "small" amount of an inflammable gas, presumed to be ethylene, remained after all of the carbon monoxide had been absorbed.[3] Long reported that the ethylene composition of the gaseous product of this reaction remained between 24 and 25% despite increases in the potassium hydroxide concentration from about 0.8 to 2.5 *N*, with a simultaneous increase in water concentration from about 8 to 40%.[4] Mossler found that the analogous reaction of chloroform yielded a gaseous mixture of 25 ± 0.5% ethylene and 75 ± 0.5% carbon monoxide regardless of whether the potassium hydroxide was 0.16, 0.8 or 3.2 *N*, whether the ethanol was absolute or mixed with an equal amount of water and whether the chloroform or alkali was in excess.[5] Although

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[1] From the M.S. Thesis of Hans Wagner (1951), and the Ph.D. Thesis of E. L. Pollitzer (1953).

[2] M. Hermann, *Ann.*, **95**, 211 (1855).

[3] H. Bassett, *ibid.*, **132**, 54 (1864).

[4] H. Long, *ibid.*, **194**, 23 (1878).

[5] G. Mossler, *Monatsh.*, **29**, 373 (1908).