[CONTRIBUTION FROM THE PIONEERING RESEARCH DIVISION, QUARTERMASTER RESEARCH AND ENGINEERING CENTER, U. S. ARMY]

The Reductive Cleavage of Ozonides to Alcohols

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Compounds with ethylenic groups have been ozonized and these ozonized materials, without prior isolation, have been treated with sodium borohydride and lithium aluminum hydride. These reagents reductively cleave the ozonized material to alcoholic products. All previous work on the reduction of ozonides with metal hydrides is also summarized.

In recent years there has been an increased interest in the reductive cleavage of ozonized compounds. Recent reports have shown that lithium aluminum hydride reductively cleaves ozonides to alcohols in good yield.[1-4]

In certain instances the high reactivity of lithium aluminum hydride might be undesirable. In the course of work in this laboratory the applicability of sodium borohydride as a milder reagent for the reductive cleavage of ozonides was investigated in addition to further experiments utilizing lithium aluminum hydride.

The only reported reduction of an ozonide with sodium borohydride is the work of Witkop and Patrick[5] who treated the ozonide of 2-phenylskatole with both lithium aluminum hydride and sodium borohydride and obtained different decomposition products.

Ozonolysis products, when reductively decomposed by reagents other than metal hydrides, yield aldehydes or ketones with yields generally ranging from poor to fair.[6] The metal hydrides give good yields of alcohols. The procedure has value both as a preparative and characterizing reaction and is summarized as follows:

$$\mathrm{R{-}CH{=}CH{-}R'} \xrightarrow[\text{2 metal hydride}]{\text{1 Ozone}} \mathrm{R{-}CH_2OH + R'CH_2OH}$$

Tables I and II summarize the results utilizing sodium borohydride and lithium aluminum hydride, respectively. The tables include all of the reported reductions of ozonides with metal hydrides. The yields of purified products have varied from 46 to 79% in our work, but since most of the experiments were run only once and some on a small scale, it is felt that these yields can be improved. No attempt was made to isolate the smaller cleavage product, methanol, from compounds I, II, III, and VIII, or the expected ethylene glycol from compound VI. The products of the reductive decomposition reaction are the same with either sodium borohydride or lithium aluminum hydride, except in those cases where the original compound has substituents which behave differently with these reducing agents, *e.g.*, oleic acid, as follows:

$$\begin{tikzcd}
 & \mathrm{CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH} \arrow[d, "O_3"] & \\
 & \text{[ozonide]} \arrow[dl, "\mathrm{NaBH_4}"'] \arrow[dr, "\mathrm{LiAlH_4}"] & \\
\mathrm{CH_3(CH_2)_7CH_2OH} + \mathrm{HOCH_2(CH_2)_7COOH} & & \mathrm{CH_3(CH_2)_7CH_2OH} + \mathrm{HOCH_2(CH_2)_7CH_2OH}
\end{tikzcd}$$

TABLE I

RESULTS OF REACTIONS OF OZONIZED COMPOUNDS WITH SODIUM BOROHYDRIDE

No.	Compound	Product 1	Yield, %	Product 2	Yield, %
I	1-Octene	1-Heptanol	74	[a]	
II	1-Hexadecene	1-Pentadecanol	79	[a]	
III	1,1-Diphenylethylene	Benzohydrol	74	[a]	
IV	Cyclohexene	1,6-Hexanediol	63		
V	Oleic acid	1-Nonanol	63	9-Hydroxynonanoic acid	46
VI	Cinnamyl alcohol	Benzyl alcohol	63	[a]	
VII	2-Phenyl-3-methylindole[b]	1-(2-Benzamidophenyl)-ethanol	93		

[a] No attempt to isolate. [b] Ref. 5.

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(1) M. Hinder and M. Stoll, *Helv. Chim. Acta*, **33**, 1308 (1950).

(2) W. Voser, D. E. White, H. Heusser, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **35**, 830 (1952).

(3) F. L. Greenwood, *J. Org. Chem.*, **20**, 803 (1955).

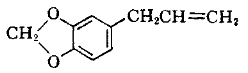
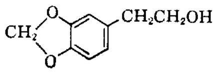
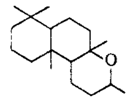
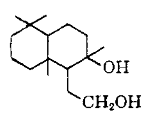
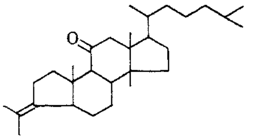
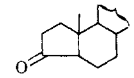
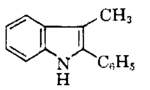
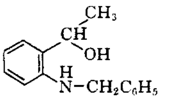
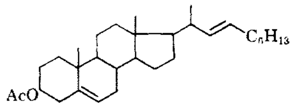
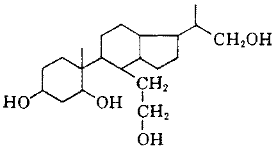
(4) H. Lettré and D. Hotz, *Angew. Chem.*, **69**, 267 (1957).

(5) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **74**, 3855 (1952).

(6) For a comprehensive review of different decomposition methods, see P. S. Bailey, *Chem. Revs.*, **58**, 925 (1958).

TABLE II

RESULTS OF REACTIONS OF OZONIZED COMPOUNDS WITH LITHIUM ALUMINUM HYDRIDE

No.	Compound	Product 1	Yield, %	Product 2	Yield, %
I	$CH_3(CH_2)_5CH{=}CH_2$	$CH_3(CH_2)_5CH_2OH$	70, 93[a]	[b]	
VIII			61	[b]	
V	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	$CH_3(CH_2)_7CH_2OH$	79	$HOCH_2(CH_2)_7CH_2OH$	50
IX	$CH_3(CH_2)_3CH{=}CH{-}CH_2CH_3$[a]	$CH_3(CH_2)_3CH_2OH$	87	$CH_3CH_2CH_2OH$	87
X	$CH_3(CH_2)_3CH{=}CH{-}CH_3$[a]	$CH_3(CH_2)_3CH_2OH$	89	CH_3CH_2OH	21
XI	 [c]		17.5		
XII	 [d]				
VII	 [e]		72		
XIII	 [f]		60		

[a] Ref. 3. [b] No attempt to isolate. [c] Ref. 1. [d] Ref. 2, product obtained after reoxidation of the alcoholic intermediate. [e] Ref. 5. [f] Ref. 4.

With sodium borohydride the terminal acid group remains unaffected, but with the more reactive lithium aluminum hydride the acid group is reduced.

Reductive cleavages with sodium borohydride. With the experimental technique employed there is no need to isolate the ozonide itself, since the reductive decomposition is carried out directly with the ozonized solution. This lessens any hazards usually associated with the isolation of pure ozonides. Most of the common solvents which have been utilized for ozonations can be employed. We have used carbon tetrachloride, chloroform, ether and iso-octane. The reductive cleavage takes place in a heterogeneous solvent system, *e.g.*, a carbon tetrachloride solution of the ozonide and an aqueous alcoholic solution of sodium borohydride. Good contact between solutions is maintained by rapid stirring with a Hershberg type stirrer. The initial reaction is carried out at or below room temperature and a heating period after the initial combination of reactants improves the yields of alcoholic products. In the case of octene-1 the alcoholic cleavage product was obtained only after the reaction mixture was warmed to 50°.

In general, ozonides will decompose in aqueous media to yield aldehydes or ketones and carboxylic acids. Although aldehydes are reduced to alcohols with sodium borohydride, carboxylic acids are unaffected by this reagent except in a special catalyst system.[7] The breakdown of the ozonide to yield initially an acid which will then resist reduction results in a lowering of yield of the alcohol. However, initial breakdown to an aldehyde will not, in effect, lower the yield of alcohol. In an alkaline aqueous system decomposition to aldehydes is favored, and when sodium borohydride is dissolved in water some of the slightly alkaline BO_2^- ion is formed. Sodium borohydride does not cleave epoxides,[8] and there is not adequate information on the behavior of peroxides with sodium borohydride. For the present, the course of the borohydride decomposition is ambiguous.

Reductive cleavages with lithium aluminum hydride. To avoid the necessity of isolating the ozonide when lithium aluminum hydride is to be used to effect reductive cleavage, the ozonolysis should be performed in a solvent which is compatible with lithium aluminum hydride. This limits the choice of solvents to ethers and hydrocarbons. Ether has not been recommended as a solvent for ozonolysis as it leads to explosive peroxide formation. However, we used ether without incident. The use of this solvent was not considered objectionable, since the

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(7) H. C. Brown and Rao Subba, *J. Am. Chem. Soc.*, **78**, 2582 (1956).

(8) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, N. Y., 1956, p. 673.

peroxides are in solution and are broken down in the reaction with the metal hydrides.

The course of the reaction probably follows the sequence discussed by Gaylord[9] in which the initial reaction involves cleavage of the peroxide linkage, followed by subsequent reduction of the carbonyl intermediates.

EXPERIMENTAL

Materials. The starting materials were commercially obtained, and their purity was checked by either melting point, refractive index, and/or infrared spectrum. The oleic acid was a clear Fisher U.S.P. liquid.

Ozonations. The ozonator was a modified version of the type described by Henne and Perilstein.[10] Most of the compounds were ozonized at a rate of 0.015 mol. ozone/hr. using 8% ozone by volume. The course of many of the ozonations was determined by removing aliquots periodically and recording their infrared spectrum, and noting the disappearance of the C=C stretching frequency at *ca.* 6.2 μ. This technique is useful with compounds which do not react rapidly with ozone, and in which case the end point is difficult to determine by the potassium iodide absorption trap method. This latter technique was used in some experiments.

A typical procedure, utilizing 1-hexadecene and a sodium borohydride reductive cleavage, is described below. The other reactions are summarized.

Sodium borohydride reductive cleavage reactions. 1-Hexadecene (II). 1-Hexadecene (5.0 g., 0.022 mol.) was dissolved in 50 ml. chloroform (reagent grade) and ozonized at −20°. The end point was determined by recording the infrared spectrum at intervals, and following the decrease in intensity of the C=C stretching absorption band at 6.5 μ. At the termination of the ozonation, new bands were present at 9.0–9.48 μ, characteristic of some ozonides.[11,12] The ozonide solution was transferred to a 2-l. 3-necked round-bottom flask equipped with a Hershberg stirrer, a condenser through which a thermometer was suspended into the flask, and an addition funnel. Sodium borohydride (Metal Hydrides Co., 98% purity) (6.69 g., 0.177 mol.) dissolved in 50 ml. cold 50% aqueous ethanol was added slowly to the stirred ozonide mixture. The temperature was maintained at 25° by occasional ice bath cooling. The reaction mixture was then warmed in a water bath for 2.5 hr. with continued stirring. After standing overnight at room temperature, the mixture was acidified with 10% sulfuric acid, the chloroform layer separated, and the aqueous layer further extracted with chloroform. The combined extracts were dried over anhydrous magnesium sulfate, filtered, and the chloroform removed by warming in a stream of nitrogen. The residue was recrystallized from aqueous ethanol to a constant m.p. of 43.8° sharp, lit.[13] 44°. The infrared spectrum was identical with a reference spectrum of 1-pentadecanol. The yield of purified product was 4.01 g. (79.0%).

1-Octene. This compound (2.5 g., 0.022 mol.) was ozonized in 25 ml. chloroform at −20° and the end point was determined by disappearance of the 6.15 μ band of the infrared spectrum of the reaction mixture. The reductive cleavage was carried out with an 8 to 1 ratio of sodium borohydride to compound at 0°, followed by a 1-hr. heating period at 50°. Heptyl alcohol in 74% yield was obtained by ether extraction, n^{20} = 1.4240, lit.[14] n_D^{20} = 1.4245. The infrared spectrum of the product was identical with that of an authentic specimen.

Cyclohexene (IV). Cyclohexene (1.50 g., 0.018 mol.) in 25 ml. chloroform was ozonized at 0° until the 6.2 μ band in the infrared spectrum of the reaction mixture disappeared. The resinous ozonide was dissolved by addition of absolute ethanol and then decomposed with sodium borohydride as in the previous experiments. The acidified reaction mixture was evaporated almost to dryness in a Rinco rotating evaporator. The residue was taken up in a slight amount of water, made basic with dilute sodium hydroxide, and extracted with chloroform. The residue after evaporation of the chloroform was recrystallized from aqueous ethanol to a constant melting point, 42.0–42.5°, lit.[15] 42°. The yield of 1,6-hexanediol was 63%.

Oleic acid. The ozonation was carried out with oleic acid (5.0 g., 0.018 mol.) in 50 ml. chloroform at 0°. A rapid color change in a potassium iodide trap after the reaction flask indicated the end point. The ozonide was cleaved as in the hexadecene reaction. The acidified reaction mixture was extracted with ether and the ether solution washed with dilute sodium hydroxide. 1-Nonanol was obtained in 62.3% yield from the ethereal portion, with n_D^{20} = 1.4334, lit.[16] n_D^{20} = 1.4338. The infrared spectrum was identical to an authentic spectrum and the *N*-phenylcarbamate derivative melted at 68.5–69.0°, lit.[17] 69°. Ether extraction of the reacidified aqueous basic solution yielded a white solid residue which after recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) afforded material melting at 49.5–51.0°, lit.[18] 51–51.5°. A neutralization equivalent gave a value of 174.2. Calculated for 9-hydroxynonanoic acid $(C_9H_{18}O_3)$, neut. equiv. = 176.8.

Cinnamyl alcohol (VI). The ozonation was carried out with cinnamyl alcohol (5.0 g., 0.037 mol.) in 50 ml. ether at 0° to the calculated end point. The reductive decomposition was carried out as in the hexadecene reaction. Ether extraction of the acidified reaction mixture yielded a liquid residue which on distillation afforded a 63.1% yield of benzyl alcohol. The infrared spectrum of the product was identical with that of an authentic specimen, and the product had n_D^{20} = 1.5396, lit.[19] n_D^{20} = 1.53955.

1,1-Diphenylethylene (III). 1,1-Diphenylethylene (2.0 g., 0.011 mol.) was ozonized in 20 ml. iso-octane at 0° with the stoichiometric quantity of ozone as determined by potassium iodide assay. The ozonide, which had precipitated, was redissolved by the addition of *p*-dioxane, and the solution then reductively decomposed as in the hexadecene reaction. The reaction mixture was evaporated in a Rinco rotating evaporator at 50° *in vacuo*. The slushy residue was redissolved in a minimum of water and this solution extracted with ether, from which was obtained a solid residue. Three recrystallizations from ether–petroleum ether (b.p. 30–60°) afforded 1.52 g. (74%) of diphenyl carbinol, m.p. 68.0–68.5°, lit.[20] 68–69°.

Lithium aluminum hydride reductive cleavage reactions. 3,4-Methylenedioxy-1-allylbenzene (VIII). 3,4-Methylenedioxy-1-allylbenzene (3.0 g., 0.018 mol.) was dissolved in 20 ml. dry ether and ozone passed through the solution at 0° for the theoretical time (as determined by potassium iodide assay). The ozonide was decomposed at 0° by slowly adding

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[9] Reference 8, p. 686–687.

[10] A. L. Henne and W. L. Perilstein, *J. Am. Chem. Soc.*, **65**, 2183 (1943).

[11] R. Criegee, A. Kerchow, and H. Zinke, *Chem. Ber.*, **88**, 1878 (1955).

[12] P. S. Bailey and S. B. Mainthia, *J. Org. Chem.*, **23**, 1089 (1958).

[13] A. Gascard, *Ann. chim. (Rome)*, **15**, 332 (1921).

[14] M. L. Sherrill, *J. Am. Chem. Soc.*, **52**, 1982 (1930).

[15] R. D. Haworth and W. Perkin, *J. Chem. Soc.*, 598 (1894).

[16] V. J. Harding and C. Weizmann, *J. Chem. Soc.*, 304 (1910).

[17] S. M. McElvain, *The Characterization of Organic Compounds*, revised edition, The Macmillan Co., New York, 1953, p. 202.

[18] P. Chitt and J. Hausser, *Helv. Chim. Acta*, **12**, 463 (1929).

[19] J. Meisenheimer, *Ber.*, **41**, 1420 (1908).

[20] F. Y. Wiselogle and H. Sonneborn, *Org. Syntheses*, **Coll. Vol. 1**, H. Gilman and A. H. Blatt, eds., John Wiley & Sons, New York, 1941, p. 90.

to a 3-fold (stoichiometric)[3] excess of lithium aluminum hydride in ether with stirring in an apparatus adequately protected from atmospheric moisture. The reaction mixture was then further decomposed by addition of 5 ml. water followed by 45 ml. 15% sulfuric acid. The product, 3,4-methylenedioxyphenylethyl alcohol, was obtained in 62% yield by ether extraction, followed by distillation, n_D^{20} = 1.5500, lit.[21] n_D^{20} = 1.5478. The phenylurethan derivative was prepared and melted at 96.6–97.0°, lit.[22] 96.4–97.0°.

Oleic acid. Oleic acid (5.0 g., 0.018 mol.) was ozonized in 40 ml. *n*-heptane solution by a procedure similar to that described in the previous paragraph. The ozonide precipitated and ether was added to obtain a solution which was then reductively decomposed with lithium aluminum hydride. Ether extraction followed by distillation *in vacuo* afforded the two cleavage products. A 79.4% yield of 1-nonanol with n_D^{20} = 1.4334, lit.[16] n_D^{20} = 1.43347 was obtained. The infrared spectrum of the product was identical with that of an authentic specimen. 1,9-Nonanediol obtained in 49.5% yield melted at 44.2°, lit.[23] 45.5°.

1-Octene (I). 1-Octene (2.5 g., 0.022 mol.) was ozonized in 25 ml. carbon tetrachloride at 0°. The solvent was evaporated at room temperature in a current of nitrogen. The residual liquid was dissolved in dry ether and reductively decomposed as in the preceding reaction. Heptanol in 70% yield was obtained by ether extraction, n_D^{20} = 1.4240, lit.[14] n_D^{20} = 1.4245. The infrared spectrum of the product was identical with that of an authentic specimen.

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(21) F. Semmler and K. Bartelt, *Ber.*, **41**, 2752 (1908).

(22) A. L. Bluhm, Ph.D. thesis, Boston University, 1957.

(23) R. Scheuble and E. Loebl, *Monatsh.*, **25**, 1081 (1904).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY SECTION, DIVISION OF CHEMISTRY, NATIONAL BUREAU OF STANDARDS]

Complexes of Diols with Cuprammonium Reagent

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The chelates present in cuprammonium solutions of methyl α-D-galactopyranoside, sucrose, di-D-fructopyranose 1,2′:2,1′-dianhydride, and the *cis*- and *trans*-1,2-cyclohexanediols have been studied by measurements of optical rotation and optical density, and the results evaluated by the method of continuous variation. In each case, a compound having a copper to diol ratio of 2:1 was found. Under the conditions stipulated, there is no evidence of compounds having a copper to diol ratio of 1:1.

The reaction of cuprammonium reagent and the diol groupings of carbohydrates has found extensive practical and theoretical use. Nevertheless, despite the importance of the reaction, the complexes formed have not been isolated and little has been reported on their structures.

The present investigation had its beginning in some measurements of optical rotation conducted by Isbell and Snyder on dextrans in cuprammonium solution.[1] The optical rotation varied widely with the concentrations of both the dextran and the copper reagent. In order to obtain some understanding of this behavior, it seemed desirable to investigate the composition and structure of cuprammonium–diol complexes. Isbell and his associates[2] have shown that in the carbohydrate-borate system, at least three diol-borate complexes exist. For practical and theoretical reasons, copper complexes derived from sucrose, methyl α-D-galactopyranoside, di-D-fructopyranose 1,2′:2,1′-dianhydride, and the *cis*- and *trans*-1,2-cyclohexanediols were selected for the investigation. The cuprammonium compounds from these compounds were studied by measurements of optical rotation (at 436 mμ) and optical density (at 350 mμ).

Measurements conducted with a photoelectric spectropolarimeter revealed a dependence of optical rotation on the proportions of both the diol and the copper reagent in the solution. The results indicated that *two moles of copper reagent react with each molar equivalent of the diol grouping.* This observation was substantiated by examination of optical density employing the method of continuous variation.

Discussion of previous work. Cuprammonium solution presumably contains di-, tri-, tetra-, and penta-ammonia complexes of copper. Bjerrum[3] has determined the stability constants of the four copper–ammonia cations and has shown that, in the presence of excess ammonia (as for the cuprammonium solutions used in the present study), the copper–tetrammonium complex $[Cu(NH_3)_4^{++}]$ greatly predominates.

In 1857, Schweizer[4] published the observation that cellulose disperses in cuprammonium solution. Since then, many practical applications of this reaction have been made.[5] The cuprammonium ion exists only in solutions having a high concentration of ammonia. Therefore, the conditions for forming a complex with a diol are restricted to a limited range of *p*H. Upon acidification, the com-

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(1) H. S. Isbell and C. F. Snyder, unpublished work (contained in NBS Report 2400, March 31, 1953).

(2) H. S. Isbell, J. Brewster, N. B. Holt, and H. L. Frush, *J. Research Natl. Bur. Standards*, **40**, 129 (1948).

(3) J. Bjerrum, *Chem. Revs.*, **46**, 381 (1950).

(4) E. Schweizer, *J. prakt. Chem.*, **72**, 109, 344 (1857).

(5) E. Heuser, *The Chemistry of Cellulose*, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 161.