Ozonolysis of Cyclic Olefins

J. E. FRANZ,[1] W. S. KNOWLES, AND C. OSUCH

Research Department, Organic Chemicals Division, Monsanto Company, St. Louis, Missouri 63177

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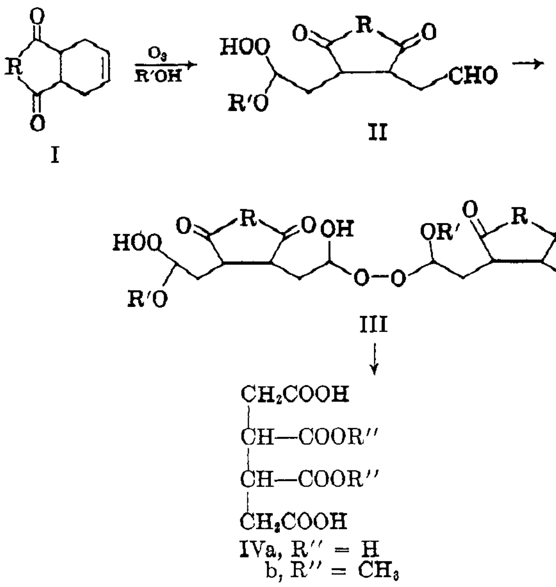
In a recent communication[2] the nitric acid oxidation of cyclic olefins to dicarboxylic acids was described. We now wish to report similar transformations of tetrahydrophthalic acid derivatives and hexachlorodicyclopentadiene using ozone as an oxidizing agent.

Our work closely parallels the ozone cleavages of cyclic olefins[3] in that all the products are adequately accounted for by the Criegee mechanism. Treatment of *cis*-Δ^4-tetrahydrophthalic acid (Ia)[4] and its anhydride Ib with ozone in a participating solvent followed by peracid oxidation gave excellent yields of *meso*-1,2,3,4-butanetetracarboxylic acid (IVa) (see Scheme I).

SCHEME I



CH_2COOH—CH—$COOR''$—CH—$COOR''$—CH_2COOH

a, R = diacid
b, R = anhydride
c, R = dimethyl ester
d, R' = CHO
e, R' = CH_3
f, R' = $COCH_3$
g, R' = H

Attempts were made to air oxidize[5] the ozonolysis products under a variety of conditions, but in no case was the yield better than 37%.

During the course of our work, we studied the structures of some of the ozonolysis intermediates. Ozonization of Ic in methanol at 0° gave a product with 1 mole of active oxygen/mole of Ic which lost half its peroxidic activity on warming to 25°. The viscous oily product obtained on removal of solvent had an infrared spectrum, molecular weight, and active oxygen content consistent with structure V. Further evidence is provided by the p.m.r. spectrum (Figure 1.) which showed no free aldehyde and protons from high to low field in the approximate ratio of 8:4:1:8:18:2:2. The eight high-field protons are ascribed to the four methylene groups in the backbone of V. The four hydrogens centered at 2.87 p.p.m. are the CH groups adjacent to the carbomethoxy functions, and the nine methoxyls are accounted for by the total of the three singlet bands at 3.56, 3.33, and 3.17 p.p.m. Finally, the four low-field protons represent the remaining hydrogen atoms of the acetal functions. A structure similar to V has been proposed[6] for one of the products obtained by ozonolysis of cyclohexene in methanol. Whereas trimethyl phosphite only partially reduced V obtained at 25°, almost complete reduction of the initially formed monomeric hydroperoxide IIce was realized at −50°, giving the methanol hemiacetal of 3,4-dicarbomethoxyadipic aldehyde (VI). This structure was confirmed by its infrared spectrum, by its conversion to a crystalline 2,4-dinitrophenylhydrazone, and by performic acid oxidation to 3,4-dicarbomethoxyadipic acid IVb (Scheme II).

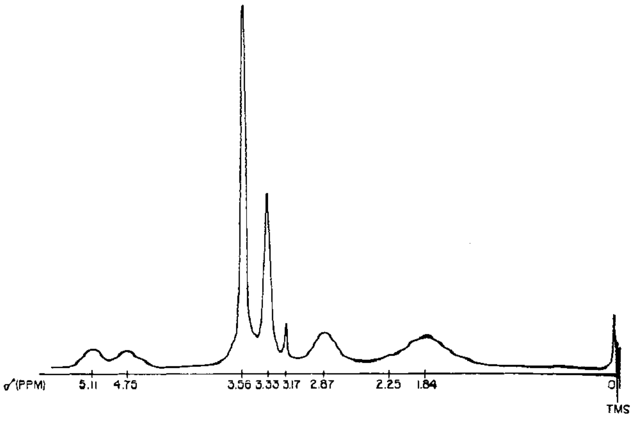


Figure 1.—P.m.r. spectrum of *cis*-Δ^4-dimethyltetrahydrophthalate ozonolysis product (V) in deuteriochloroform (slow sweep).

Ozonization of Ib in 98% formic acid produced a gelatinous product which slowly dissolved with loss of active oxygen. Performic acid oxidation of the deactivated solution gave IVa in 85% yield. Alternatively, addition of ether precipitated a white solid whose analysis, molecular weight, and neutralization equivalent are consistent with a formic acid adduct of 2,3-dicarboxyadipic aldehyde.[7] Reduction[8] and solvolysis[9] of ozonolysis products by formic acid have been reported previously. In contrast to the results obtained in formic acid, the ozonolysis product of Ib in acetic acid was relatively stable on storage.

Ozonolysis of the acid Ia in acetonitrile at 0° produced a solution containing 1 equiv. of active oxygen. There was apparently no solvent participation and the isolated product gave the correct analysis for a dimeric

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[1] To whom inquiries should be sent.

[2] J. E. Franz, J. Herber, and W. S. Knowles, *J. Org. Chem.*, **30**, 1488 (1965).

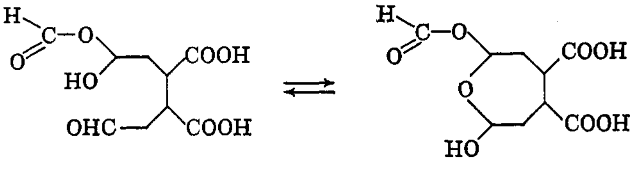
[3] P. Bailey, *Chem. Rev.*, **58**, 925 (1958).

[4] M. Fremery and E. Fields, *J. Org. Chem.*, **28**, 2537 (1963).

[5] P. Bailey, *Ind. Eng. Chem.*, **50**, 993 (1958).

[6] P. Bailey, *J. Org. Chem.*, **22**, 1548 (1957).

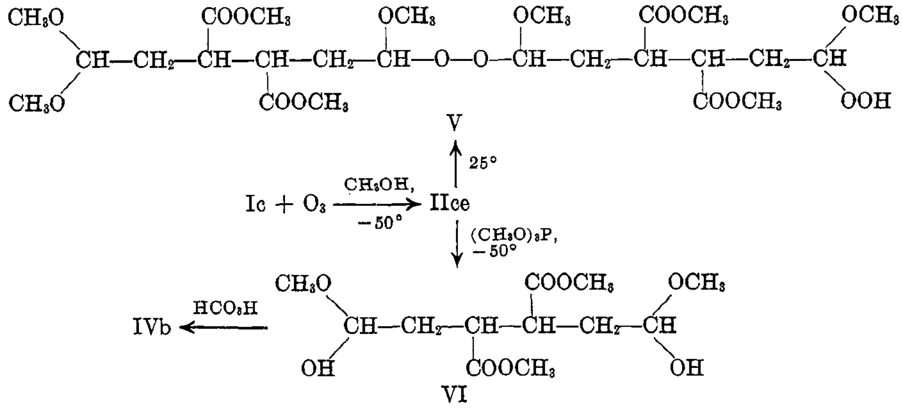
[7] The structure of this product is not known. A ring-stabilized hemiacylal is proposed.



[8] R. Dorland and H. Hibbert, *Can. J. Res.*, **B18**, 30 (1940).

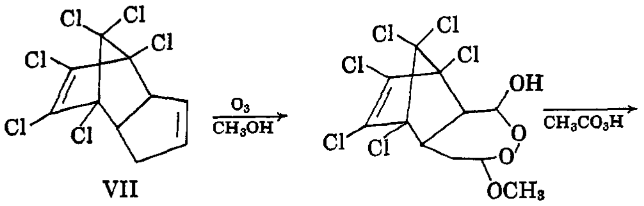
[9] E. Bernatek and T. Ledaal, *Tetrahedron Letters*, **No. 26**, 30 (1960).

SCHEME II



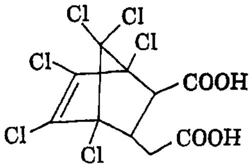
ozonide.[10] Performic acid oxidation of the latter product yielded IVa in 93% yield. In a similar manner norbornylene[11] in acetonitrile solvent gave a mixture of ozonides which appeared to be partially hydrated dimers.

In methanol–methylene chloride solution hexachlorodicyclopentadiene (VII) slowly absorbed 1 mole of ozone without appreciable attack at the highly hindered double bond of the norbornylene skeleton. The crude product, obtained in quantitative yield, consisted of a 1:1 mixture of a stable crystalline solid (VIII)[12] and a viscous oil. The infrared spectrum of the solid had strong bands at 2.9 and 6.3 μ consistent with hydroxyl and norbornene functions but no carbonyl absorption. Strong bands were also observed in the 11.5–12.3-μ region. Molecular weight and elemental analysis corresponded to an empirical formula $C_{11}H_{10}Cl_6O_4$. Peracetic acid oxidation yielded a mixture of dibasic acids. The major product of this oxidation (IX) melted at 221–222° and gave the correct analysis for $C_{10}H_6Cl_6O_4$. A similar product,[13] m.p. 200°, has been prepared in low yield by the nitric acid oxidation of hexachlorodicyclopentadiene. The stereochemistry of these products is unknown at the present time.



VII

VIII



IX

Experimental Section[14]

Ozonolysis Products of *cis*-Δ⁴-Tetrahydrophthalic Anhydride.—Ozonization of 0.1 mole of Ib in 60 ml. of 98% formic acid at room temperature produced a white precipitate which had neut. equiv. 86 and an active oxygen content of 3.86%. When allowed to remain in formic acid for several hours, the product slowly dissolved, and the resulting solution was devoid of active oxygen. Addition of ether to the deactivated formic acid solution resulted in precipitation of a white amorphous solid melting with decomposition at 110–125°.

Anal. Calcd. for $C_9H_{12}O_8$: C, 43.57; H, 4.88; neut. equiv., 83; mol. wt., 248. Found: C, 44.15; H, 4.62; neut. equiv., 87; mol. wt., 287.

The data correspond approximately to a formic acid derivative[7] of 2,3-dicarboxyadipic aldehyde. Oxidation of this product with performic acid gave IVa in 85% yield.

Oxidation of Ozonolysis Products to *meso*-1,2,3,4-Butanetetracarboxylic Acid. Performic Acid Method.—The suspension obtained on ozonization of 15.2 g. (0.1 mole) of Ib in 60 ml. of 98% formic acid at room temperature was heated to 50° and treated with 105 ml. (0.9 mole) of 30% hydrogen peroxide at 65–75°. The solution was then heated to reflux and an additional 20 ml. of peroxide was added. The colorless solution was concentrated to dryness and the white crystalline residue was washed with ether and air dried. The yield of IVa was 22 g. (95%), m.p. 188–190°.

Peracetic Acid Method.—A solution of 0.05 mole of ozonolysis product prepared in 30 ml. of glacial acetic acid was slowly heated to 100° during 4 hr. with 15 g. (0.1 mole) of 53% peracetic acid. After work-up there was obtained 10 g. (86%) of tetrabasic acid IVa, m.p. 184–190°.

Oxygen Method.—A solution of 15 g. (0.1 mole) of Ib in 100 ml. of 90% acetic acid[15] was ozonized at 90° and then further treated with a stream of oxygen at 90° for 2 hr. After remaining overnight at room temperature, the yield of precipitated IVa was 8.7 g. (37%), m.p. 186–189°. An oil (12.5 g.) was recovered from the acetic acid filtrate.

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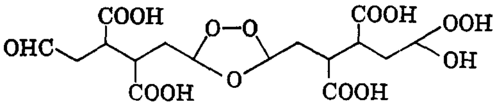
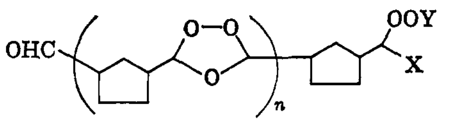
[10] Presumably the product $C_{16}H_{22}O_{15}$ has the following structure analogous to that obtained from norobornylene.[11]



[11] R. Perry [*J. Org. Chem.*, **24**, 829 (1959)] has prepared ozonides of norbornylene in other inert solvents and proposes the following structure.



The "gum" and "precipitate" products described by Perry are consistent with his analyses when X is hydroxyl, Y is hydrogen, and *n* is 5 and 10, respectively. In acetonitrile our results indicate a similar structure with *n* close to unity (*i.e.*, $C_{14}H_{22}O_7$).

[12] VIII may also be the product in which the hydroxyl and methoxyl groups are interchanged. The stereochemistry is unknown.

[13] R. Riemschneider, *Chem. Ber.*, **89**, 2697 (1956).

[14] Melting points are uncorrected. The ozone source was a Welsbach T-23 ozonator. Infrared spectra were obtained using a Perkin-Elmer Infracord spectrophotometer, Model 137. P.m.r. spectra were run on a Varian HR-60 at 60 Mc./sec. with tetramethylsilane as reference.

[15] No tetrabasic acid was obtained when the ozonization and air oxidation were carried out in formic acid. This result is in direct contrast to that reported[6] for the air oxidation of cyclohexene ozonolysis products in which best yields of adipic acid were obtained in formic acid solvent.

The air oxidation of ozonolysis products of Ia, Ib, and Ic to tetrabasic acid derivatives was studied in detail. Varying the temperature from 25 to 100°, the use of several solvents (methanol, isopropyl alcohol, formic acid, acetic acid, propionic acid, acetone, and water) and various catalysts (zinc oxide, ammonium metavanadate, manganese dioxide, potassium permanganate, cobalt acetate, palladium on charcoal, and bromine) never gave yields better than 37%. Higher oxygen pressures and ultraviolet light were not beneficial. The use of chlorine[16] as an oxidizing agent also gave poor results.

Ozonolysis of Dimethyl *cis*-Δ⁴-Tetrahydrophthalate (Ic).—A solution of 19.8 g. (0.1 mole) of dimethyl ester Ic in 60 ml. of methanol readily absorbed 0.1 mole of ozone at 0–10°. Immediate titration of the cold solution indicated that 1 equiv. of active oxygen was present. After concentration *in vacuo* the residual oil (28.8 g.) had a molecular weight of 572; infrared bands at 2.9, 5.75, and 11.1–11.5 μ; and an active oxygen content of 3.17% (57% of the original solution). These data coupled with the p.m.r. spectrum (Figure 1, hydroxyl protons replaced with deuterium) are consistent with the dimeric structure V.

3,4-Dicarbomethoxyadipic Acid (IVb).—The ozonolysis product of 20 g. (0.1 mole) of ester Ic (prepared in 60 ml. of methanol) was dissolved in 100 ml. of 98% formic acid and further oxidized with a 6% stream of ozone at 65–95° (MnO_2 catalyst). After removal of the solvent, the semisolid was triturated with ether to yield IVb (5 g.). An analytical sample was obtained from ethyl acetate, m.p. 147–148°.

Anal. Calcd. for $C_{10}H_{14}O_8$: C, 45.80; H, 5.39; neut. equiv., 131. Found: C, 45.67; H, 5.57; neut. equiv., 131.

3,4-Dicarbomethoxyadipic Aldehyde Hemiacetal (VI).—The ozonolysis product of Ic made in methanol at −50° was treated with 1 equiv. of trimethyl phosphite[17] at −50°. The resulting product was an oil which could not be distilled without decomposition. A 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized from ethanol–dimethylformamide, m.p. 230–231°.

Anal. Calcd. for $C_{22}H_{22}N_8O_{12}$: C, 44.74; H, 3.76. Found: C, 45.04; H, 4.19.

Performic acid oxidation of VI (15 g.) gave IVb (9 g.). In addition there was obtained an oil (5 g.), neut. equiv. 136, which appeared to be a mixture of isomeric 1,2,3,4-butanetetracarboxylic acid dimethyl esters. Saponification yielded tetrabasic acid IVa.

Ozonization of *cis*-Δ⁴-Tetrahydrophthalic Acid in Acetonitrile.—A mixture of 5.3 g. (0.03 mole) of Ia and 40 g. of acetonitrile absorbed 1 equiv. of ozone at 0°. Immediate titration of the cold solution indicated that 1 equiv. of active oxygen was present. Concentration *in vacuo* followed by thorough drying of the residual powder gave a product free of acetonitrile.

Anal. Calcd. for $C_{16}H_{22}O_{15}$[10]: C, 42.3; H, 4.8. Found: C, 42.4; H, 5.1.

One gram of ozonide yielded 0.9 g. (93%) of IVa (m.p. 186–189°) when refluxed with 5 ml. of 30% hydrogen peroxide and 5 ml. of 98% formic acid.

Ozonization of Norbornylene in Acetonitrile.—Ozonization of a mixture of 4 g. (0.04 mole) of norbornylene and 40 g. of acetonitrile at −10 to −30° resulted in a white gelatinous precipitate. After remaining overnight at room temperature, the product (2 g.) was collected and washed with ether. The acetonitrile filtrate yielded 3.2 g. of an easily pulverizable foam after concentration to a final pressure of 0.2 mm.

Anal. Calcd. for $C_{14}H_{22}O_7$[11]: C, 55.60; H, 7.25. Found: C, 55.2, 54.7; H, 7.20, 7.38.

Ozonization of Hexachlorodicyclopentadiene (VII).—A mixture of 33.9 g. (0.1 mole) of hexachlorodicyclopentadiene,[18] 50 ml. of methanol, and 70 ml. of methylene chloride was cooled to −5°. A 6% ozone stream was admitted to the agitated solution for 3 hr. during which time a slow absorption of ozone occurred. The solution was concentrated *in vacuo* and the semisolid residue (42.6 g.) was mixed with 25 ml. of 98% formic acid. The insoluble crystalline product (21 g., 50%) VIII[12] was collected by filtration and washed with formic acid, m.p. 164° dec. An analytical sample was prepared by recrystallization from benzene. The sample was unchanged after storage for 1 year.

Anal. Calcd. for $C_{11}H_{10}Cl_6O_4$: C, 31.46; H, 2.41; Cl, 50.65; mol. wt., 419. Found: C, 31.61; H, 2.53; Cl, 50.25; mol. wt., 397.

After concentration of the formic acid filtrate there was recovered 21 g. (50%) of viscous oil. This product was not further investigated.

The crystalline ozonolysis product (1 g.), commercial 40% peracetic acid (3 g.), and 4 ml. of acetic acid were heated at 50° for 6 hr. and then allowed to remain overnight at room temperature. After removal of solvent, there was obtained 1 g. of crude product. Recrystallization from water–methanol yielded 0.6 g. of dibasic acid (IX), m.p. 221–222°.

Anal. Calcd. for $C_{10}H_6Cl_6O_4$: C, 29.81; H, 1.50; Cl, 52.80; neut. equiv., 201. Found: C, 29.84; H, 1.86; Cl, 52.55; neut. equiv., 197.

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[16] L. C. King and H. Farber, Abstracts, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1959, p. 89P.

[17] W. S. Knowles and Q. E. Thompson, *J. Org. Chem.*, **25**, 1031 (1960).

[18] R. Riemschneider, *Monatsh.*, **83**, 802 (1952); M. Livar, P. Klucko, and M. Paldan, *Tetrahedron Letters*, **No. 3**, 141 (1963).

On the Reaction of Grignard Reagents with β-Tertiary Amino Ketones

RICHARD BALTZLY

Wellcome Research Laboratories, Tuckahoe, New York

AND JOHN W. BILLINGHURST

Wellcome Chemical Research Laboratories,
Beckenham, Kent, England

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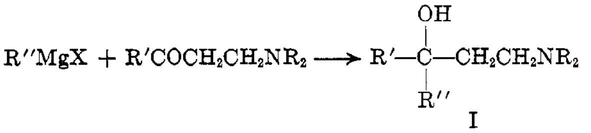
A considerable number of amino alcohols of the general type I have been prepared by the action of



$$R''MgX + R'COCH_2CH_2NR_2 \longrightarrow R'\text{—}\overset{OH}{\underset{R''}{C}}\text{—}CH_2CH_2NR_2 \qquad (1)$$

I

Grignard reagents on the appropriate Mannich bases.[1] Although generalization is rather difficult because the yields obtained by various authors are not always comparable, it is evident that in many cases the yields were surprisingly poor. For the case where R'' = cyclohexyl and R' = phenyl, leading to the commercially important compounds Trihexyphenidyl and Tricyclamol [NR_2 = $N(CH_2)_5$ and $N(CH_2)_4$, respectively], Adamson[1c] suggested that the loss could be due to reduction of the ketone (competing with the addition of the reagent). Since, however, considerable quantities (of the order of 30%) of Mannich base are at times recoverable,[2] it appears more likely that the major loss was due to enolization. This should be especially serious with reagents such as the cyclohexylmagnesium halides which are known to be sluggish in addition. It is consistent with this interpretation that Ruddy and Buckley,[1b] who employed a considerable variety of Grignard reagents and Mannich bases, reported that their yields were much better when there was alkyl substitution on the carbons between the carbonyl and the amino group. Such substitution could not be expected to facilitate addition, but it would be expected to diminish enolization.

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(1) (a) J. J. Denton, *et al.*, *J. Am. Chem. Soc.*, **71**, 2050, 2053, 2054 (1949); (b) W. A. Ruddy and J. S. Buckley, *ibid.*, **72**, 718 (1950); (c) D. W. Adamson, P. A. Barrett, and S. Wilkinson, *J. Chem. Soc.*, 52 (1951); (d) D. W. Adamson, *ibid.*, S-144 (1949); 885 (1950).

(2) E. M. Bottorff, private communication.