[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

The Ozonolysis of Indene in Ethanol

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The use of ethanol as a solvent for selective ozonolysis has been explored using indene. No true ozonide was isolated; the product has been shown to be 3-hydroxy-4,5-benzo-7-ethoxy-1,2-dioxacycloheptane. Its structure was established by conversion to 3,7-diethoxy-4,5-benzo-1,2-dioxacycloheptane, homophthalic acid, homophthaldehyde, homophthalyl alcohol, o-carboxyphenylacetaldehyde and 1-isochromanone.

The cleavage of olefins by ozone is usually carried out in two steps: reaction with ozone in an inert solvent to form ozonides and subsequent oxidation or reduction in the presence of water or acetic acid. Since ozonides are somewhat unstable,[2] have variable composition,[3] form polymeric ozonides,[4,6] disproportionate,[5] and because occasionally other oxidations occur during the reaction of olefins with ozone–oxygen mixtures,[2-4] ozonolyses have been carried out in glacial acetic acid which presumably reacts with the ozonide as soon as it is formed; however, the primary reaction product has not been characterized.

Until recently, alcohols have seldom been employed as solvents for ozonizations because of their ease of oxidation.[6,7] However, methanol has been used by a number of investigators[8-10] and also a *t*-butyl alcohol–sulfuric acid medium has been employed in studies on the mechanism of ozonolysis.[11]

In the present work, the use of absolute ethanol as a solvent for ozonolysis was found to be possible because passage of a stream of 3% ozone in oxygen through 500 ml. of absolute ethanol for one hour at 0–5° produced less than 0.1 mole of acetic acid, 0.03 mole of peroxide and 0.01 mole of acetaldehyde. This slight attack made it possible to explore the use of ethanol as a solvent, using an olefin, indene, which reacted rapidly and selectively with 3% ozone.

Ozonolysis of 0.1 mole of indene in absolute ethanol at 0–5° was complete in one hour; removal of the alcohol left a 99% yield of a white, non-explosive compound melting at 105–108°. Analytical data gave the formula $C_{11}H_{14}O_4$ and showed one ethoxyl group and one peroxide grouping. Infrared analysis indicated the presence of a hydroxyl group and an acetal linkage but the complete absence of any carbonyl. No oxygen was liberated when this product was treated with lead tetraacetate which indicates that the peroxide grouping is not –OOH but must be of the ROOR type.[12] The most probable structure is shown by formula I which is analogous to the structure assigned by Bailey[9] to the product obtained by ozonolysis of phenanthrene in methanol. This structure also provides a reasonable explanation of the degradation products shown in Chart I.

The acid-catalyzed reaction of I with ethanol yielded the diethoxy compound II. Alkali converted both compounds I and II to *o*-carboxyphenylacetaldehyde (VIII). The structure of the latter was shown by: (a) solubility in dilute alkali, (b) positive Benedict test, (c) formation of a monosemicarbazone, and (d) reduction of the aldehyde group to the alcohol by means of either sodium borohydride or aluminum isopropoxide and loss of water to yield the lactone, 1-isochromanone (IX). The properties of the latter agreed with those given by Wegler and Frank[13] but differed from the properties of 3-isochromanone prepared by Murahashi.[14] The formation of IX shows that the carboxyl group of VIII is attached to the ring and not to the side chain.

The oxidation of both peroxy compounds I and II with hydrogen peroxide produced homophthalic acid (III) in good yield. The homophthalic acid was identified by converting it into 1,3(2,4)-isoquinolinedione[15] by heating its ammonium salt.

Reduction of the peroxide I with zinc dust and a trace of acetic acid at room temperature produced homophthalaldehyde[16] (IV), an oil, which was characterized by the formation of its bis-*p*-nitrophenylhydrazone. This dialdehyde IV when treated with zinc dust and acetic acid at 80° was further reduced to *o*-hydroxymethylphenylacetaldehyde (V). Reduction of the hydroperoxide I with lithium aluminum hydride in ether produced a nearly quantitative yield of homophthalyl alcohol[17] (VI). This compound on refluxing with a trace of sulfuric acid was converted completely into isochroman[17] VII.

This use of ethanol as a solvent for ozonolysis not only avoids the handling of explosive ozonides but also furnishes a stable intermediate I valuable for the synthesis of compounds IV through IX which are otherwise difficult to obtain.

Experimental

3-Hydroxy-4,5-benzo-7-ethoxy-1,2-dioxacycloheptane (I).—The indene was purified by fractionally distilling it twice

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[1] United States Public Health Post-Doctoral Fellow 1955–1956.

[2] L. Long, *Chem. Revs.*, **27**, 437 (1940).

[3] J. E. Leffler, *ibid.*, **45**, 385 (1949).

[4] C. S. Marvel and V. Nichols, *J. Org. Chem.*, **6**, 296 (1941).

[5] R. Criegee, *Ann.*, **583**, 1 (1953).

[6] F. L. Greenwood, *J. Org. Chem.*, **10**, 414 (1945).

[7] C. Harries, *Ann.*, **343**, 311 (1906); **374**, 288 (1910).

[8] E. Briner and D. Frank, *Helv. Chim. Acta*, **21**, 1297 (1938); R. Criegee and G. Lohaus, *Ann.*, **583**, 6 (1953); E. I. duPont de Nemours and Co., British Patent 709,450 [*C. A.*, **50**, 401 (1956)].

[9] P. S. Bailey, THIS JOURNAL, **78**, 3811 (1956).

[10] At the International Conference on Ozone, Chicago, Ill., Nov. 28–30, 1956, a considerable number of ozonolyses in methanol and methanol–methylene chloride mixtures were reported.

[11] N. A. Milas, P. Davis and J. T. Nolan, Jr., THIS JOURNAL, **77**, 2536 (1955).

[12] R. Criegee, H. Pilz and H. Flygare, *Chem. Ber.*, **72**, 1799 (1939); R. Criegee, *Fortschr. Chem. Forsch.*, **1**, 536 (1950).

[13] R. Wegler and W. Frank, *Ber.*, **70B**, 1279 (1937).

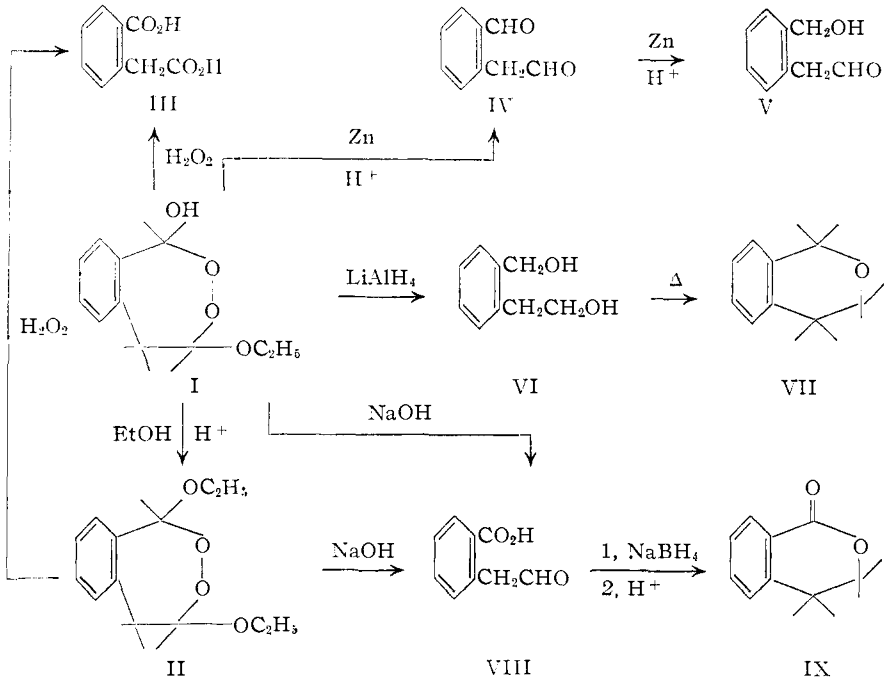
[14] S. Murahashi, *Sci. Papers, Inst. Phys. Chem. Res.* (*Tokyo*), **30**, 180 (1936).

[15] Buu-Hoi, *Bull. soc. chim.*, **12**, 313 (1945).

[16] T. Zincke and F. Krollpfeiffer, *Ann.*, **408**, 314 (1915).

[17] S. Siegel and S. Coburn, THIS JOURNAL, **73**, 5494 (1951).

CHART I



at 10 mm. pressure, and storing it at −3° until used. A solution of 11.6 g. (0.1 mole) of indene in 500 ml. of anhydrous ethanol was cooled in an ice-bath and a 3% stream of ozone in oxygen was passed through the solution for 55 minutes. When the ozonization was carried out under the above conditions, only a trace of unreacted ozone passed through the ethanol into the potassium iodide trap during the reaction. The potassium iodide trap was changed once or twice during the experiment and thus the end-point of the reaction was easily detectable by the sudden liberation of iodine in the trap. The flow rate of ozonized oxygen was 80 l./hr.

The peroxide I was isolated by concentrating the ethanol solution to dryness under vacuum at room temperature. The weight of white, solid, amorphous product was 21 g. (99%), m.p. 105–108° (softens 95–105°). The product was not crystalline but was similar to paraffin wax in appearance. It did not decompose explosively when subjected to a variety of thermal and physical shocks.

Analysis of the peroxide I for active oxygen was carried out by the following method. The peroxide, approximately 0.001 mole, was dissolved in 25 ml. of glacial acetic acid, and 2 g. of potassium iodide and 1 ml. of concentrated hydrochloric acid were added. The solution was warmed to 50–70° for 10 minutes, poured into 400 ml. of water and the liberated iodine titrated with standard sodium thiosulfate solution. Infrared absorption curves obtained in Nujol paste showed a peak at 3.05 μ and broad peaks at 9.30 and 9.65 μ.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71; active oxygen, 7.61; ethoxyl, 21.4; mol. wt. 210.2. Found: C, 63.17; H, 6.56; active oxygen, 7.53; ethoxyl, 21.0; mol. wt. (cryoscopic), 214.

The Criegee[12] lead tetraacetate test for the hydroperoxy grouping was carried out by treating 1 g. of the compound I in 25 ml. of glacial acetic acid with 3 g. of lead tetraacetate in 50 ml. of glacial acetic acid. No evolution of oxygen occurred. Control tests with peracetic acid and ethyl hydroperoxide were positive.

CAUTION: Absolute ethanol has been used satisfactorily as a solvent in over 25 ozonolyses without the formation of explosive products. However, only a dilute (3%) stream of ozone in oxygen, and temperatures of 0–5° have been employed for selective ozonolyses of olefins. Use of 9–10% ozone leads to attack of aromatic nuclei and more concentrated ozone–oxygen mixtures should be investigated with great caution.[18]

During the ozonolysis the exit gases from the reaction flask appeared as a dense white smoke. The amount of smoke produced can serve as a method for following the progress of the reaction; as the concentration of unreacted olefin in the solvent decreases so does the volume of smoke produced. When vapors of indene at 182° were mixed with a stream of 3% ozone in oxygen, again copious amounts of dense white colloidal particles were produced. These may possibly arise from the polymerization of intermediates in the vapor phase. These colloidal particles could not be removed from the gas stream by either a Dry Ice trap or by passing the vapors through various solvents. The colloidal particles were removed from the gas stream by a small copper grid charged to approximately 25,000 volts with a Tesla coil. The actual weight of material in the smog was too small to permit purification and identification.

3,7-Diethoxy-4,5-benzo-1,2-dioxacycloheptane (II).—To a solution of 21 g. (0.1 mole) of the peroxide I in 500 ml. of anhydrous ethanol was added 3 drops of concentrated sulfuric acid. The anhydrous solution was kept at room temperature for 24 hours and the solution was evaporated to dryness under vacuum. The precipitate was filtered, washed with water and after recrystallization from either acetone or glacial acetic acid, there resulted 15.5 g. (65%) of white needles, m.p. 80–81°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61; active oxygen, 6.72; ethoxyl, 37.8. Found: C, 65.42; H, 7.41; active oxygen, 6.72; ethoxyl, 37.3.

Homophthalic Acid (III).—To a solution of 3.0 g. of the peroxide I in 20 ml. of acetic acid was added 30 ml. of 15% hydrogen peroxide. After warming to 60° for 10 hours the mixture was concentrated to 20 ml. by boiling and upon cooling, crystals of homophthalic acid separated. Recrystallization from acetic acid gave 1.6 g. of material, m.p. 180°. Homophthalic acid also was obtained from the diethoxy compound II under similar conditions.

For the large-scale preparation of homophthalic acid it was preferable to carry out the ozonization reaction in glacial acetic acid. The acetic acid was removed under vacuum leaving a non-explosive viscous colorless sirup.

This sirup could not be obtained analytically pure. However, the gain in weight corresponded to the combination of one mole of indene with one mole of ozone plus one mole of acetic acid. It contained approximately one peroxy group and one acetoxy group indicating that this product of ozonolysis in acetic acid may be an acetoxy derivative analogous to compound I. Treatment of the sirup with hot aqueous sodium carbonate and hydrogen peroxide followed by acidification gave an 82% yield of homophthalic acid, m.p. 180°. The latter was identified by conversion to 1,3-(2,4)-isoquinolinedione, m.p. 233°, by heating the ammonium salt as described by Buu-Hoi.[15] Both compounds I and II were also converted to homophthalic acid by refluxing with dilute nitric acid for one hour.

Homophthalaldehyde (IV).—A solution of 21 g. (0.1 mole) of compound I in 500 ml. of ethanol, 50 ml. of water and 15 ml. of acetic acid was vigorously stirred while 10 g. of zinc dust was added in 1-g. amounts approximately every six minutes. After one hour the reaction mixture was filtered to remove the zinc dust and evaporated to dryness under vacuum. The residue, a yellow gum, was mixed with 50 ml. of water and ether extracted. The ether layer was washed with dilute sodium carbonate solution and dried over sodium carbonate. Evaporation of the ether gave homophthalaldehyde, 14.5 g. (98%), as a yellow oil. This aldehyde is very unstable since it undergoes self-condensation.

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(18) M. L. Kilpatrick, C. C. Herrick and M. Kilpatrick, THIS JOURNAL, **78**, 1784 (1956).

It was identified as homophthalaldehyde by treating 1 g. of the oil with excess *p*-nitrophenylhydrazine and isolating the bis-*p*-nitrophenylhydrazone derivative in quantitative yield. Recrystallization from 80% ethanol gave orange crystals, m.p. 220–221°. The literature[16] listed the m.p. as 185–190°; hence an elemental analysis was obtained.

Anal. Calcd. for $C_{21}H_{18}N_6O_4$: C, 60.28; H, 4.34; N, 20.09. Found: C, 60.29; H, 4.39; N, 19.83.

***o*-Hydroxymethylphenylacetaldehyde** (V).—A solution of 14.8 g. (0.1 mole) of homophthaldehyde in 100 ml. of ethanol was stirred vigorously with 200 ml. of 50% acetic acid and an excess of zinc dust for 2 hours at 80°. The zinc dust was added in 1-g. quantities to maintain a constant suspension in the solution. The mixture was filtered and evaporated to dryness under vacuum leaving a yellow gum. This was mixed with 100 ml. of water and ether extracted. The ether solution was washed with dilute sodium carbonate solution and dried over sodium carbonate. Upon evaporation of the ether, *o*-hydroxymethylphenylacetaldehyde was obtained as a yellow oil, b.p. 116–120° (5 mm.), $n^{25}D$ 1.5240.

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.03; H, 7.22.

Homophthalyl Alcohol (VI).—To a solution of 20 g. of lithium aluminum hydride in 200 ml. of ether was slowly added 21 g. (0.1 mole) of the peroxide I over a 30-min. period. The solution was vigorously stirred under reflux for an additional 20 minutes and water was added slowly to decompose the excess lithium aluminum hydride. The solution was acidified with 25% sulfuric acid, and the water and ether layers were separated. The water solution was ether extracted with an additional 200 ml. of ether and the ether extracts were combined, washed with dil. sodium carbonate solution, and dried over sodium carbonate. Removal of the ether under vacuum gave 14.5 g. (95%) of colorless oil of homophthalyl alcohol.[17] Identification of the oil was carried out by treating 1 g. of the oil with excess *p*-nitrobenzoyl chloride in pyridine to form the di-*p*-nitrobenzoate derivative, m.p. 134–135°.

Anal. Calcd. for $C_{23}H_{18}O_8N_2$: C, 61.33; H, 4.03; N, 6.22. Found: C, 61.36; H, 4.32; N, 6.24.

Isochroman VII.—The distillation of homophthalyl alcohol at 70° (3 mm.) with a drop of sulfuric acid gave a nearly quantitative yield of isochroman and water. Redistillation yielded a fraction boiling 69–70° at 3 mm. The isochroman[17] was a colorless liquid; m.p. 3–4°, $n^{20}D$ 1.5422, $d^{25}{}_4$ 1.0707.

Anal. Calcd. for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.42; H, 7.26.

***o*-Carboxyphenylacetaldehyde** (VIII).—A solution of 21 g. (0.1 mole) of the peroxide (I) in 200 ml. of ethanol was warmed with 200 ml. of 5% sodium hydroxide solution. The mixture turned a dark red as an exothermic reaction occurred and the temperature rose to 50°. The alkaline solution was kept at this temperature for 20 minutes, acidified with acetic acid, and concentrated to a viscous oil under vacuum. The oil was dissolved in ether and extracted with cold 1 *N* sodium hydroxide. Careful neutralization of the alkaline solution with dilute acetic acid precipitated yellow crystals of *o*-carboxyphenylacetaldehyde, 14.7 g. (90%), m.p. 130–140°. This substituted phenylacetaldehyde is unstable and the melting point decreased with standing and the compound finally became an oil. This probably accounts for the range of melting and for the fact that the m.p. observed in this work is higher than that previously reported by Schopf and Kuhne.[19] The semicarbazone derivative melted sharply at 209–210° and analyzed correctly.

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.28; H, 5.06; N, 19.34.

The compound VIII differed from the known isomeric *o*-formylphenylacetic acid[20] whose semicarbazone melts at 220°.

1-Isochromanone (IX).—A solution of 16.4 g. (0.1 mole) of *o*-carboxyphenylacetaldehyde in 200 ml. of isopropyl alcohol was refluxed with 400 ml. of isopropyl alcohol and 82 g. (0.4 mole) of aluminum isopropoxide for 9 hours. The apparatus was arranged with a fractionating column which permitted the slow distillation of acetone and isopropyl alcohol (200 ml.) during the reaction. The solution was evaporated to dryness under vacuum, mixed with 200 ml. of 6 *M* sulfuric acid, and ether extracted. The ether extract was washed with water, dried over sodium sulfate, and evaporated under vacuum. The residue, a yellow oil, was vacuum distilled to yield 12 g. (79%) of 1-isochromanone, b.p. 148–150° (5 mm.), $n^{25}D$ 1.5622, $d^{25}{}_4$ 1.1996; Wegler and Frank[13] report a b.p. of 165° (16 mm.).

Reduction of *o*-carboxyphenylacetaldehyde with excess sodium borohydride in water at 30–40° also gave 1-isochromanone in 40% yield.

Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.44; H, 5.21.

Acknowledgment.—The authors wish to thank Dr. Philip S. Bailey for valuable suggestions in interpreting these results.

[19] C. Schopf and R. Kuhne, *Ber.*, **83**, 390 (1950).

[20] J. O. Halford and B. Weissmann, *J. Org. Chem.*, **18**, 30 (1953).

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Tetrachloroisoindolines and Related Systems. Alkylation Reactions and Inductive Effects[1]

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The basicity of an isoindoline nitrogen atom is profoundly affected by inductive factors. Four chlorine atoms on the four available positions of the benzene ring or a positively charged nitrogen atom β to the isoindoline nitrogen decrease the reactivity of the isoindoline nitrogen toward alkylation. These effects cannot be results of resonance interaction and are, therefore, either steric (unlikely) or inductive (most probable). These conclusions, based on observations of alkylation behavior under certain conditions, are supported by pK_a determinations which are consistent with relative basicities of model amines. Stabilities of quaternized nitrogens, especially those with bromoethyl substituents, are also discussed.

The interesting physiological action of the ganglionic blocking agent 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline dimethochloride (VIIb)[2] has focused attention on the tetrachloroisoindoline system itself. Although isoindolines have been considered[3] typical amines, the alkyla-

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[1] Presented before the 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956.

[2] Ecolid (CIBA Trade Mark). See A. J. Plummer, J. H. Trapold, J. A. Schneider, R. A. Maxwell and A. E. Earl, *J. Pharmacol. Exptl. Therap.*, **115**, 172 (1955). An alternative name for VIIb, which can be extended to related isoindolines, is 4,5,6,7-tetrachloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium dichloride. The term "ammonio" was originally proposed by J. F. Bunnett and co-workers [*Chem. Revs.*, **49**, 291 (1951); THIS JOURNAL, **75**, 642 (1953)]. It has also been mentioned in A. M. Patterson's column on Nomenclature in *Chem. Eng. News*, **32**, 2320 (1954); **33**, 5262 (1955). It is used in this paper for the tetrasubstituted terminal nitrogen.

[3] D. R. Boyd and D. E. Ladhams, *J. Chem. Soc.*, 2089 (1928).