Notes A department for short papers of immediate interest.

A Convenient Method for Reduction of Hydroperoxidic Ozonation Products

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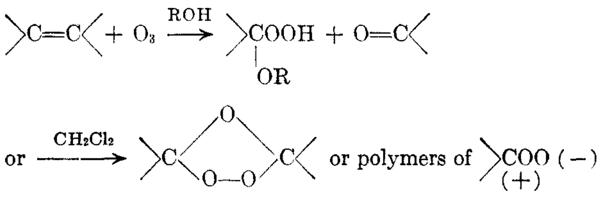
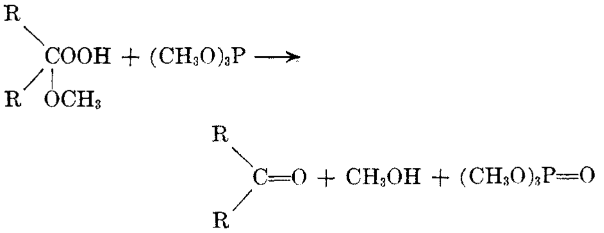
Criegee and co-workers[1] have shown that, in general, the ozonolysis of olefins in hydroxylic solvents gives rise to hydroperoxides plus a carbonyl fragment, whereas use of inert (nonparticipating) solvents results in the formation of ozonides and polymeric peroxides.



Many reducing agents[2] and procedural variations have been employed for converting the products of ozonolysis (usually without regard to their structure) to neutral carbonyl fragments. In general, catalytic hydrogenation, reduction with metal-acid combinations and with acidified iodide ion have been most widely utilized.

Experience in this laboratory has indicated that aldehydic and ketonic materials are best obtained by effecting ozonolysis at low temperatures (−40° or below) in a hydroxylic solvent, usually methanol, followed immediately by reduction at the lowest possible temperature. One of the principle failings of present reduction methods has been insufficient activity at low temperatures.[3] The lower trialkyl phosphite esters rapidly reduce the hydroperoxidic[4] ozonation products to the corresponding carbonyl compounds at temperatures around −40°



$$R_2C(OCH_3)OOH + (CH_3O)_3P \longrightarrow R_2C{=}O + CH_3OH + (CH_3O)_3P{=}O$$

In addition to rapidity and convenience, this procedure has wide applicability and has, in our hands, generally proved equal or superior to older methods It is well suited for characterization purposes. One may obtain derivatives of the carbonyl fragments merely by adding the appropriate reagent to the methanol solution following completion of the low temperature ozonolysis and reduction steps. The trialkyl phosphate formed as the coproduct is relatively inert and does not interfere with the formation of carbonyl derivatives Results obtained when this technique was applied to a number of readily available laboratory olefins are shown in Table I. Generally the yields compare favorably with those obtained using other methods, although the yield of benzaldehyde from *trans*-stilbene was inferior to that (93%) previously reported.[5,6]

On the other hand, 1,4-butyndiol diacetate was converted to the corresponding dione diacetate in somewhat better yield than the 35% reported by Criegee and Lederer.[7]

The phosphite reduction method was less advantageous when isolation of the free carbonyl compounds was required, as it was necessary to choose a phosphite ester with physical properties such that neither it nor its corresponding phosphate would interfere in the isolation procedure. Trimethyl phosphite was used most often in the present investigation. Reduction of cyclohexene-methanol ozonation products with triethyl, triisopropyl, and tri-*n*-butyl phosphites proceeded equally well.

In order to ascertain something of the reactivity of trimethyl phosphite with various other peroxidic materials obtained by ozonolysis of olefins, reaction with the intermediates obtained from the ozonolysis of phenanthrene in methanol was investigated. The structures of these intermediate

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[1] (a) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958); (b) R. Criegee, *Record of Chemical Progress*, **18**, 111 (1957) for excellent discussion of this work.

[2] See reference 1a and an earlier review by L. Long, *Chem. Rev.*, **27**, 437 (1940) for a more complete enumeration of these reducing agents.

[3] R. H. Perry, *J. Org. Chem.*, **24**, 829 (1959).

[4] Reduction of simple *tert*-alkyl hydroperoxides by triethyl phosphite has been previously observed by I. S. Bengelsdorf *et al.*, Abstr. 134th Meeting American Chemical Society, Chicago, Illinois, 1958, paper No. 115, p. 69P and by C. Walling, Abstr. 16th National Organic Symposium, Seattle, Washington, 1959, p. 88. See also D. B. Denney, W. F. Goodyear, and B. Goldstein. *J. Am. Chem. Soc.*, **82**, 1393 (1960) and references cited therein.

[5] A. Maggiolo, *Organic Ozone Reactions and Techniques*, The Welsbach Corporation, Ozone Process Division, Philadelphia, Pa., 1957.

[6] L. A. Subluskey, G. C. Harris, A. Maggiolo, and A. Tumolo, paper presented at International Ozone Conference, Chicago, Illinois, November 28–30, 1956; *Advances in Chem. Ser.*, **21**, 149 (1958).

[7] R. Criegee and M. Lederer, *Ann.*, **583**, 29 (1953).

TABLE I

REDUCTION OF OZONATION HYDROPEROXIDES WITH TRIMETHYL PHOSPHITE

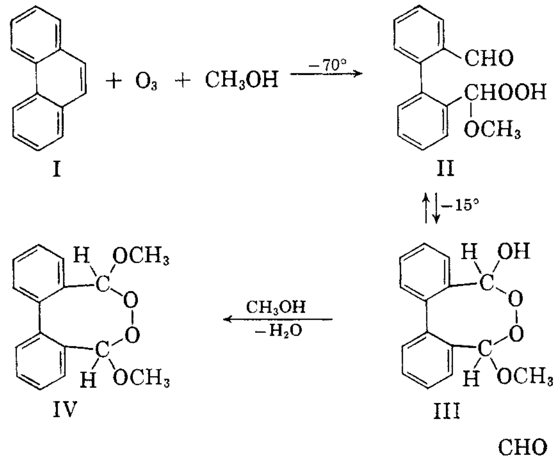
Olefin	Carbonyl product	Yield (%)	Isolated as	M.P.
Cyclohexene	Adipaldehyde	85	Disemicarbazone	193–195°[a]
3-Methylcyclohexene	3-Methyladipaldehyde	77	Di-*p*-nitrophenylhydrazone	163–164°[b]
trans-Stilbene	Benzaldehyde	84	Semicarbazone	220–222°[c]
Indene	Homophthalaldehyde	65	Di-*p*-nitrophenylhydrazone	218–220°[d]
Phenanthrene	2,2′-Diphenyldicarboxaldehyde	100	Di-*p*-nitrophenylhydrazone	265–266° dec.[e]
Dibutyl maleate	Butyl glyoxylate	78	Semicarbazone	220–222°[f]
Cinnamic acid	Benzaldehyde	86	Semicarbazone	220–222°[c]
	Glyoxylic acid	30	Semicarbazone	209–210°[g]
Phenylacetylene	Phenylglyoxal	40	Di-*p*-nitrophenylhydrazone	310–312°[h]
1,4-Butynediol acetate	1,4-Diacetoxy-1,2-butanedione	65	Di-*p*-nitrophenylhydrazone	290–310° dec.[i]

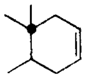
[a] A. Wohl and H. Schweitzer, *Ber.*, **39**, 895 (1906) have reported 206°. [b] *Anal.* Calcd. for $C_{19}H_{22}N_6O_4$: C, 57.28; H, 5.57; N, 21.1. Found: C, 57.25; H, 5.57; N, 21.0. [c] F. J. Wilson, I. M. Heilbron, M. M. J. Sutherland, *J. Chem. Soc.*, **1914**, 2905 give m.p. 221° dec. [d] J. L. Warnell and R. L. Shriner, *J. Am. Chem. Soc.*, **79**, 3165 (1957) report 220–221°. [e] *Anal.* Calcd. for $C_{26}H_{20}N_6O_4$: C, 64.99; H, 4.20; N, 17.49. Found: C, 64.83; H, 4.31; N, 17.46. [f] *Anal.* Calcd. for $C_7H_{13}N_3O_3$: C, 44.91; H, 7.00; N, 22.45. Found: C, 44.78; H, 6.84; N, 22.69. [g] E. Muller, *Ber.*, **47**, 3021 (1914) has reported m.p. 207°. [h] F. Straus reports 310–311°, *Ann.*, **393**, 292 (1912). [i] *Anal.* Calcd. for $C_{20}H_{20}N_6O_8$: C, 50.85; H, 4.27; N, 17.79. Found: C, 51.10; H, 4.45; N, 18.00.

products have been elucidated by Bailey[8] and by Wibaut.[9] Presumably, the first material in the low temperature ozonolysis is the open hydroperoxide II. At about −15°, however, the cyclic hemiacetal III appears to be the principle product. On standing in methanol at room temperature, III is converted to the peracetal IV.

When the clear phenanthrene ozonation solution at −70° was treated with trimethyl phosphite, vigorous reduction occurred and a quantitative yield of the dialdehyde was obtained as its di-*p*-nitrophenylhydrazone. Identical results were obtained when ozonolysis was carried out at −15°. On the other hand, IV was found to be stable for many days in trimethylphosphite at room temperature. As it is likely that III was in equilibrium with the open form, these results indicate that probably only the hydroperoxy function (—OOH) is effectively reduced by the phosphite. This assumption was further supported by the observation that cyclohexene ozonized at −60° using inert solvents (methylene chloride-acetonitrile) gave an ozonolysis mixture which was attacked only slightly by trimethylphosphite, even at room temperature.

The contraction of a six-membered ring D cyclohexene to the corresponding cyclopentene carboxaldehyde was a cardinal feature of Woodward's classical steroid synthesis.[10] Whether this ring contraction was carried out on tricyclic[10,11] or tetracyclic[12] intermediates, the path was multistep and laborious, as it required hydroxylation of V (osmium tetroxide[10] or silver acetate-iodine[11,12]) to VI, protection of the glycol (except in one case[12]), and finally cleavage with periodic acid and cyclization of the dialdehyde (VII) to VIII. At best, the over-all yield from V to VIII did not exceed 35%. Attempts in this laboratory to prepare dialdehydes of type VII by ozonolysis of V using standard workup methods were only nominally successful.[13] However, low temperature selective

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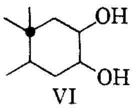
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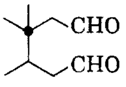
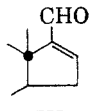
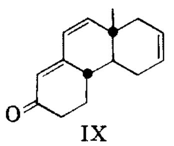
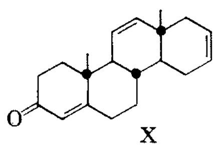

VII


VIII

a, tricyclic
b, tetracyclic


IX


X

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(8) P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956).

(9) J. P. Wibaut and T. J. DeBoer, *Rec. trav. chim.*, **78**, 183 (1959).

(10) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(11) L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **78**, 4111 (1956).

(12) L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **76**, 5014 (1954).

(13) In U. S. Patent **2,854,459** (1958) to W. S. Knowles and B. S. Wildi, the maximum over-all yields for the ring contraction steps were about 25%.

ozonolysis of the tricyclic and tetracyclic ketones IX and X in methanol followed by reduction with trimethyl phosphite yielded, after cyclization, the corresponding 5-membered ring D aldehydes (VIIIa,b) in 54% and 57% over-all yields, respectively with marked saving of time and labor over previous methods.

EXPERIMENTAL[14]

Apparatus. A Welsbach T-23 laboratory ozonizer was used. The ozone-oxygen stream was monitored by a Welsbach model C ozone meter. The ozone was delivered to an Ace Glass Mini-Lab Reactor assembly cat. No. 10104. With appropriate flow meters and potassium iodide traps, the amount of ozone delivered to a reaction mixture and the amount absorbed in a given time could be readily determined by titration of the iodine liberated by the off-gas stream.

General procedure for preparation and reduction of hydroperoxide ozonation cleavage products. Twenty-five millimoles of the olefin was dissolved in about 50 ml. of dry[15] methanol. If low temperature insolubility were encountered, an additional 50 ml. of methylene chloride[15] was also added. The solution was cooled to −65° to −70° in a Dry Ice bath and treated with a 3–4% oxygen-ozone stream until the calculated amount of ozone had been absorbed. A slow nitrogen stream was then bubbled through the cold solution and 5 ml. (about 40 mmoles) of trimethyl phosphite was added. Reduction was usually very rapid and accompanied by a marked temperature rise to around −20° even with strong cooling. Within 5 min. the reduction was complete and the solution was allowed to come to room temperature. Preparation of the carbonyl derivative was effected by addition of about 50–55 mmoles[16] of *p*-nitrophenylhydrazine or semicarbazide in methanol or other appropriate solvent, followed by heating for a short time on a steam bath.

In the case of cinnamic acid, the crude semicarbazones were collected and stirred for 30 min. with 50 ml. of cold 0.5*M* sodium hydroxide solution in order to dissolve out glyoxylic acid semicarbazone. Filtration and acidification served to isolate the latter from benzaldehyde semicarbazone.

l-(−)-anti-trans-3a,7,8,9,9a,9b-Hexahydro-3a-methyl-7-oxo-(1H)-benz[e]indene-3-carboxaldehyde (VIIIa). A solution of 2.14 g. (10 mmoles) of IX[17] was dissolved in 30 ml. of methylene chloride and diluted with 30 ml. of methanol. A standardized ozone-oxygen stream delivering 0.70 mmole of ozone per min. was added at −60° until 10 mmoles of ozone had been absorbed (14.5 min.). Addition of ozone was terminated and 3.0 ml. of trimethyl phosphite was added. A slight temperature rise was noted and the reaction mixture was allowed to come to room temperature over 1 hr. The solvents were removed *in vacuo* on a rotating drier. The clear oily residue was then heated at 60–80° at 0.5 mm. to remove phosphate esters. This crude dialdehyde was then cyclized in benzene using the piperidine-acetic acid method of Woodward.[10] A total of 1.635 g. of crude VIIIa was obtained which yielded sticky crystals on scratching. The crude product was dissolved in ether and was put through a short column of alumina. A total of 1.233 g. (54%) of almost colorless crystals, m.p. 118–123°, was obtained. Two recrystallizations from ether gave the analytical sample, m.p. 124.5–126°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.91; H, 7.06. Found: C, 79.14; H, 7.25.

(+)-Δ-9(11),16-Bisdehydro-21-norprogesterone (VIIIb). One gram (3.55 mmoles) of the (−) tetracyclic ketone X[12] was dissolved in 50 ml. of methylene chloride to which was then added 50 ml. of methanol. The solution was treated for 5.1 min. with ozone at −60° as in the previous experiment. Reduction was effected by addition of 2 ml. of trimethyl phosphite. Subsequent workup and cyclization was also effected as previously described. A first crop of 465 mg., m.p. 154–156°, of essentially pure VIIIb was obtained. Infrared assay of material in mother liquors indicated the presence of another 131 mg. The total yield of useful product amounted to 57%. Recrystallization of first crop material from isopropyl alcohol gave pure material, m.p. 160–161°, showing no melting point depression with authentic material.[12]

In an identical experiment, but with the ozonolysis carried out at 0° instead of −65°, the total yield of VIIIb was only 28%.

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[14] Melting points are uncorrected.

[15] The use of reasonably dry solvents is indicated because of sensitivity of trialkyl phosphites to water. This did not appear to be a stringent requirement, however, as solvents of reagent grade were found to be quite satisfactory.

[16] It is known that carbonyl reagents such as phenylhydrazine, *p*-nitrophenylhydrazine, or hydroxylamine will itself reduce certain ozonation products. See P. S. Bailey, *Ber.*, **87**, 993 (1954), J. P. Wibaut and J. van Dijls, *Rec. trav. chim.*, **64**, 413 (1946), L. W. F. Kampschmidt and J. p. Wibaut, *Rec. trav. chim.*, **73**, 431 (1954), P. W. Haaijman and J. P. Wibaut, *Rec. trav. chim.*, **60**, 842 (1941) and p. H. Bergman and K. DeJong, *Rec. trav. chim.*, **78**, 275 (1959) for examples of this reaction. The relatively high yields of derivative obtained using essentially no excess of reagent indicate that the carbonyl compound is not acting as a reducing agent in the present case.

[17] Q. E. Thompson, *J. Org. Chem.*, **23**, 622 (1958).

Alkylation of Amines by Esters and Lithium Aluminum Hydride

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Ethyl acetate has often been recommended[1] as a reagent for the decomposition of excess lithium aluminum hydride in lithium aluminum hydride reductions. During the preparation of 1,2-propanediamine derivatives as intermediates for our analgesic program,[2] we encountered difficulties which indicated that this reagent should be used with caution in the preparation of amines, since the addition of an ester to a mixture of an amine and lithium aluminum hydride may result in alkylation of the amine.[3]

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[1] (a) W. G. Brown, *Organic Reactions*, John Wiley and Sons, Inc., New York, N. Y., 1951, VI, p. 488; (b) M. D. Banus, *Chem. Eng. News*, **32**, 2424 (1954); (c) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, N. Y., 1956, p. 1010.

[2] (a) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959); (b) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., 135th National Meeting of The American Chemical Society, Boston, April 1959.