

Oxidative cleavage of lipids with sodium metaperiodate in pyridine

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SUMMARY The cleavage of α -diols and α -amino alcohols with sodium metaperiodate proceeds under mild conditions and in high yields when pyridine is used as reaction medium. The method is suitable for preparative as well as analytical applications.

SUPPLEMENTARY KEY WORDS α -diols · α -glycols · α -amino alcohols · sphingosine bases · *rac*-4-sphingene · *rac*-sphinganine · *cis,cis*-9,12-octadecadien-1-al (linolealdehyde) · *trans*-2-hexadecen-1-al

LEAD TETRAACETATE (1) and sodium metaperiodate (2, 3) are commonly employed for the oxidative fission of α -diols, α -amino alcohols, and some other vicinally disubstituted compounds. Cleavage with lead tetraacetate is known to lead to overoxidation and other side reactions (4, 5), whereas cleavage with sodium metaperiodate, usually in aqueous solution, proceeds with greater specificity (3). Periodate oxidation of lipophilic substances can be carried out in aqueous medium in the presence of emulsifying agents (6). In some instances reactions in acetic acid (7), aqueous methanol (8), or other mixtures of solvents (9) are satisfactory for the cleavage of certain lipids.

We have found that periodate oxidation of various vicinally disubstituted lipids proceeds specifically and quantitatively at room temperature when absolute pyridine is used as reaction medium. Pyridine is a good solvent for many lipids and offers several other advantages: the anhydrous reaction medium eliminates the light-induced formation of ozone that is known to occur when periodate oxidations are carried out in aqueous solutions (10); pyridine also prevents undesirable reactions that are likely to occur in aqueous solvents when formic acid is a product of periodate oxidation; moreover, it is known that amino alcohols are cleaved most readily in a basic medium (11).

In the present communication we describe procedures applicable to the quantitative cleavage of a variety of vicinally disubstituted lipids. The synthesis of linolealdehyde from the corresponding nonadecadiene-1,2-diol is described as an example of a preparative application of periodate oxidation in pyridine. By means of the same reaction, a variety of naturally occurring long-chain 1,2-diols, 2,3-diols, 1-alkyl glycerol ethers, 1-alk-1'-enyl glycerol ethers, and sphingosine bases can be cleaved and

subsequently analyzed as aldehydes by gas-liquid chromatography. Cleavage and analysis of sphingosine bases are described in detail as examples of an analytical application of periodate oxidations.

Thin-layer chromatography on Silica Gel G (E. Merck, A.G., Darmstadt, Germany) and on the same adsorbent impregnated with silver nitrate was employed to check the homogeneity of the final products. The plates were developed with hexane-diethyl ether 90:10 in tanks lined with filter paper. After chromatography the substances were made visible by spraying with chromic sulfuric acid solution and charring. Gas chromatography was performed with an F&M Scientific (Hewlett-Packard) instrument, model 5750, containing a column (5 ft. \times 1/4 inch I.D.) packed with 10% diethylene glycol succinate on Gas-Chrom P (Applied Science Laboratories Inc., State College, Pa.). The instrument was operated at 160°C. Helium served as carrier gas at a pressure of 54 psi. Melting points were determined on a Kofler stage under the microscope and are corrected. IR spectra were recorded with a Perkin-Elmer spectrophotometer, model 21, in carbon disulfide solution. UV spectra were obtained in a Beckman DK-2 instrument with diethyl ether as solvent.

Preparative Procedure

The synthesis of linolealdehyde from nonadecadiene-1,2-diol is described in detail.

cis,cis-9,12-Octadecadien-1-al. *cis,cis*-10,13-Nonadecadiene-1,2-diol (2.97 g, 10 mmoles), prepared from linoleoyl chloride via the diazoketone and acetyl ketol (5), 5.3 g (25 mmoles) of powdered sodium metaperiodate (No. 56072, Fluka A.G., Buchs SG, Switzerland), and 50 ml of dry pyridine are placed in a three-necked flask fitted with inlet and outlet tubes for dry nitrogen. The mixture is stirred vigorously at room temperature for 24 hr, diethyl ether and air-free water are added, and the water layer is extracted three times with ether. The combined ether phases are washed consecutively with ice-cold water, 2 N sulfuric acid (until acidic), water, 1% potassium carbonate solution (until basic), and water, and then dried over anhydrous sodium sulfate. After evaporation of the solvent in vacuo, 2.50 g of linolealdehyde with a purity of better than 95% is obtained. The aldehyde is purified by adsorption chromatography on layers of Silica Gel G, 2 mm thick (12), with hexane-diethyl ether 90:10 as developing solvent in unlined tanks.

cis,cis-9, 12-Octadecadien-1-al (1.88 g, 71%) was obtained as a colorless liquid, mp -35 to -34°C . The light-orange 2,4-dinitrophenylhydrazone was recrystallized from ethanol, and melted at $48-49^\circ\text{C}$ (reference 5, $42.5-43^\circ\text{C}$). The linolealdehyde synthesized was pure as judged by adsorption, argentation, and gas chromatography. Its retention time in gas chromatography was

2.95, relative to hexadecanal. The IR spectrum exhibited, in addition to the usual absorption bands of long-chain aldehydes, a medium strong band at 3005 cm^{-1} associated with an olefinic C-H stretching vibration, and a shoulder near 695 cm^{-1} due to the *cis*-C-H out-of-plane deformation. The C=C stretching absorption occurred near 1655 cm^{-1} . Absorption associated with *trans*-C-H out-of-plane deformation near 965 cm^{-1} was not detected. The UV spectrum did not indicate the presence of conjugated double bonds. IR spectroscopy and argentation chromatography proved that *cis-trans* isomerization and other alterations of carbon double bonds did not occur during the reaction described.

Analytical Procedure

The cleavage of α -amino alcohols is described in detail for the analysis of sphingosine bases.

A mixture of 3 mg of sphingosine bases and 30 mg of powdered sodium metaperiodate is allowed to react in 3 ml of dry pyridine for 6 hr with vigorous stirring under an atmosphere of dry nitrogen in the reaction flask. Air-free water (25 ml) is added and the mixture is extracted three times with 15 ml of hexane. The combined organic phases are washed three times with 15 ml of ice-cold water and dried over anhydrous sodium sulfate. The volume of the solution is adjusted to 3 ml by evaporation of most of the solvent in a stream of nitrogen. The concentrated solution is used for gas chromatographic analysis.

The aldehydes formed through cleavage of synthetic *rac*-4-sphingenine (DL-sphingosine) and *rac*-sphinganine¹ (DL-dihydro-sphingosine) were isolated by thin-layer chromatography and characterized as follows.

trans-2-Hexadecen-1-al was obtained by periodate cleavage of *rac*-4-sphingenine. The aldehyde, mp $27\text{--}29^\circ\text{C}$, was pure as judged by adsorption (R_f 0.43), argentation, and gas chromatography. The retention time in gas chromatography was 1.93 relative to hexadecanal. The IR spectrum of 2-hexadecen-1-al showed a strong absorption band at 1682 cm^{-1} due to vibrations of the carbonyl function in conjugation with the carbon double

bond. The stretching frequency of the latter was shifted to 1638 cm^{-1} . The *trans*-C-H out-of-plane deformation occurred at 973 cm^{-1} . *trans*-2-Hexadecen-1-al formed an orange 2,4-dinitrophenylhydrazone, mp $124\text{--}125.5^\circ\text{C}$, absorption maximum $365\text{ m}\mu$.

Hexadecan-1-al was obtained by cleavage of *rac*-sphinganine. The aldehyde, mp $32\text{--}33^\circ\text{C}$ ($33\text{--}34^\circ\text{C}$)², migrated as a single fraction in adsorption (R_f 0.54), argentation, and gas chromatography. R_f values and retention time were identical with those of a synthetic standard. The IR spectrum exhibited the bands to be expected for saturated long-chain aldehydes. Hexadecan-1-al gave a yellow 2,4-dinitrophenylhydrazone, mp $105\text{--}106^\circ\text{C}$ ($106\text{--}107^\circ\text{C}$)², absorption maximum $350\text{ m}\mu$ ($350\text{ m}\mu$)².

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¹ Sphingosine bases (Miles Laboratories Inc., Elkhart, Ind.) were purified by thin-layer chromatography on Silica Gel G, with chloroform-methanol-2 N ammonium hydroxide 75:25:1 as developing solvent and chloroform-methanol 1:1 for recovery of the samples.

² The values given in parentheses are those found for a synthetic standard prepared from hexadecyl methanesulfonate (13) by oxidation with dimethyl sulfoxide (14).