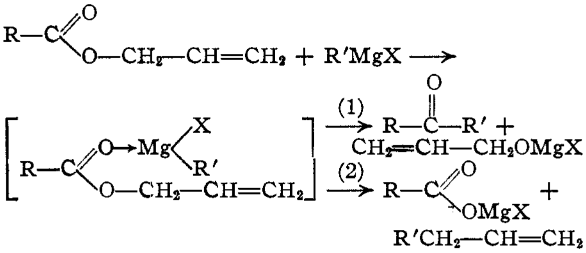
Grignard Cleavage of Allylic Esters. IV. Steric Hindrance in the Grignard Reagent

By Richard T. Arnold, R. Winston Liggett[1] and Scott Searles, Jr.[2]

A Grignard reagent may react with an allylic ester of a tertiary carboxylic acid in two ways: (1) by addition to form a ketone or an alcohol and (2) by cleavage to form an olefinic hydrocarbon and a salt of the acid. The two processes generally take place simultaneously and are the results of different modes of rearrangement of the coördination complex which is formed as the first step in the Grignard reaction.[3,4]



Unless retarded by steric hindrance the addition process (1) usually predominates over the cleavage process, as in the reaction of allyl benzoate with phenylmagnesium bromide.[5] With allylic esters of sterically hindered acids, however, it has been shown in previous communications,[4,6] that the phenyl Grignard reagent reacts chiefly by the cleavage process.[2]

It would be anticipated that the Grignard reagent may have the degree of steric hindrance required to retard the addition reaction and permit cleavage to predominate with allylic esters of unhindered acids. Actually it was found that in the reaction of mesitylmagnesium bromide with allyl benzoate, the cleavage process occurred to the extent of at least 57%,[7] while the normal addition reaction to form 2,4,6-trimethylbenzophenone proceeded to the extent of about 15%.[7] The Grignard cleavage of allylic esters due to steric hindrance in the Grignard reagent has not been reported previously.

Experimental

A Grignard solution prepared from bromomesitylene (25 g.), magnesium (3.2 g.) and ether (50 ml.) was allowed to react for eighteen hours at 25–35° with a solution of allyl benzoate (16.2 g.) in ether (50 ml.). The reaction mixture was then decomposed with slightly acidified ammonium chloride solution, and the ether solution was extracted thoroughly with sodium carbonate solution (10%). Acidification of the alkaline solution gave benzoic acid (5.1 g., 42% of theoretical); m. p. 121–121.3°.

Because of the similar boiling points of allylmesitylene and allyl benzoate, the neutral material obtained from the ether solution was saponified by refluxing four hours with alcoholic potassium hydroxide. Extraction of the mixture with water and ether and acidification of the alkaline extracts gave benzoic acid (3.2 g., corresponding to 26% recovery of unchanged allyl benzoate). Distillation of the ether layer gave allylmesitylene (5.7 g., 36%), b. p. 215–222°(737 mm.), $n^{26}\text{D}$ 1.5149, and 2,4,6-trimethylbenzophenone (2.4 g., 11%), b. p. 174° (12 mm.), $n^{21}\text{D}$ 1.5738, as well as some mesitylene (5.5 g.), as expected from the hydrolysis of unused Grignard reagent.

School of Chemistry
University of Minnesota
Minneapolis, Minnesota

Received July 12, 1948

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[1] Du Pont Post-doctorate Fellow, 1941–1942.

[2] Du Pont Predoctoral Fellow, 1946–1947. Present address: Department of Chemistry, University of Illinois.

[3] Johnson, Gilman's "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1880.

[4] Arnold, Bank and Liggett, This Journal, **63**, 3444 (1941).

[5] Gilman and Robinson, *Bull. soc. chim.*, **45**, 640 (1929).

[6] Arnold and Liggett, This Journal, **64**, 2875 (1942).

[7] Actual yield adjusted for recovery of unchanged allyl benzoate.

The Osmium Tetroxide Oxidation of Some Long-Chain Unsaturated Fatty Acids

By Alfred R. Bader

As a means of extending the evidence of the configurations of the products of oxidation of oleic, elaidic, linoleic, erucic, and brassidic acid with permanganate and peracids, a study has been made of their oxidation by osmium tetroxide. Since this reacts through a cyclic ester intermediate,[1] a *cis*-ethylene must give an *erythro* diol and a *trans* ethylene a *threo* diol. In each case the oxidation products obtained were the ones obtained also in the alkaline permanganate oxidation of the same acids. Hence the 9,10-dihydroxystearic acid melting at 132° and the 13,14-dihydroxybehenic acid melting at 132° are the *erythro*-diols, the two isomers melting at 95° and 101°, respectively, are the *threo*-diols and the eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid have the configurations assigned them by McKay and Bader.[2]

This is in accord with the work of Wittcoff and co-workers[3,4] who pointed out that the criteria (*viz.*, formation of boric acid complexes, rate of oxidation with lead tetraacetate and periodate, and rate of formation of isopropylidene compounds) which characterize *cis*-glycols in cyclic structures also characterize *threo*- rather than *erythro*-diols in straight chain compounds.

Swern[5] has criticized McKay and Bader[2] for their supposed assumption that alkaline permanganate oxidation proceeds by "*trans* hydroxylation"; this criticism is due to the use[2] of the confusing designation "*trans*" glycol to describe a compound of the *erythro* series. "*trans*" was used[2] for *erythro* and "*cis*" for *threo*, because the vicinal hydroxyl groups in *threo* diols possess a closer spatial relationship than those in *erythro* diols.[4] The present work supports the actual conclusions reached[2,3,4,5] which are the opposite of those of Hilditch and co-workers[6,7,8] and of Dorée

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[1] Criegee, *Ann.*, **522**, 75 (1936).

[2] McKay and Bader, *J. Org. Chem.*, **13**, 75 (1948).

[3] Wittcoff and Miller, This Journal, **69**, 3138 (1947).

[4] Wittcoff, Moe and Iwen, *ibid.*, **70**, 742 (1948).

[5] Swern, *ibid.*, **70**, 1239 (1948).

[6] Hilditch, *J. Chem. Soc.*, 1828 (1926).

[7] Hilditch and Lea, *ibid.*, 1576 (1928).

[8] Atherton and Hilditch, *ibid.*, 204 (1943).

and Pepper.[9] They assumed that the alkalinity of the permanganate solutions causes inversion, but in the osmium tetroxide reaction the medium is acidic throughout and yet the same products are obtained.

The author wishes to thank Professor and Mrs. L. F. Fieser for helpful advice during the course of this investigation.

Experimental

Oleic,[10] elaidic,[11] linoleic,[12] erucic[9] and brassidic[9] acids were prepared by the standard procedures. One gram lots of each were oxidized with osmium tetroxide by the method of Butenandt.[13] In each case there were obtained in about 60% yield the *hydroxyacids obtained also in the alkaline potassium permanganate oxidation* of the same acids. Their identity was established by melting point and mixed melting point. The mixture of stereoisomers melting at 156° obtained in the oxidation of linoleic acid was separated into the two isomers melting at 173° and 164°, respectively, by the method of Riemenschneider and co-workers.[14] The experimental data are summarized in Table I.

TABLE I

Compound oxidized	Crude product Wt. g.	M. p., °C.	Pure product Wt., g.	M. p., °C.	Mixed m. p., °C.
Oleic acid	0.86	126–129	0.67	132	132
Elaidic acid	.82	88–91	.62	94–95	94–95
Erucic acid	.90	124–127	.70	132	131–132
Brassidic acid	.79	94–96	.59	101	101
Lineoleic acid	.80	156–157	.28	172–173	172–173
			.17	164	164

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[9] Dorée and Pepper, *ibid.*, 477 (1942).

[10] Lapworth, Pearson and Mottram, *Biochem. J.*, **19**, 7 (1925).

[11] Bertram, *Chem. Weekblad*, **33**, 3 (1936).

[12] McCutcheon, "Organic Syntheses," **22**, 75 (1942).

[13] Butenandt, Schmidt-Thomé and Paul, *Ber.*, **72**, 1116 (1939).

[14] Riemenschneider, Wheeler and Sando, *J. Biol. Chem.*, **127**, 391 (1939).

THE CONVERSE MEMORIAL LABORATORIES
HARVARD UNIVERSITY
CAMBRIDGE, MASS.
RECEIVED JUNE 10, 1948

Chemical Degradation of Isotopic Succinic and Malic Acids[1a]

BY A. A. BENSON AND J. A. BASSHAM

The path of carbon in photosynthesis[1] may be traced by determination of the positions of labeled carbon atoms in the intermediates involved. Enzymatic degradation of succinic and malic acids have been reported[2] but require pure enzyme preparations. Unequivocal chemical degradations of these intermediates are reported in this note. Succinic and malic acids containing C^{14} were isolated from plant extracts using silica gel partition chromatography[3] and co-crystallized with convenient amounts of carrier acids.

The Curtius[4] degradation of succinic acid has been modified to give good yields on small amounts. Methyl succinate, prepared using diazomethane, is converted to the diazide through the dihydrazide.[4,5] Rearrangement of the diazide in ethanol gives ethylenediurethan which was hydrolyzed to give carbon dioxide from the carboxyl groups and ethylenediamine from the methylene groups of the original succinic acid.

$$\mathrm{HO_2C{\cdot}\overset{*}{C}H_2{-}\overset{*}{C}H_2{-}CO_2H} \xrightarrow[\text{reaction}]{\text{Curtius}}$$

$$\mathrm{C_2H_5{-}O{-}CO{-}NH{-}\overset{*}{C}H_2{-}\overset{*}{C}H_2{-}NH{-}CO{-}OC_2H_5} \xrightarrow[\text{reflux}]{48\%\ \mathrm{HBr}}$$

$$2\mathrm{CO_2} + \mathrm{H_3N^+{-}\overset{*}{C}H_2{-}\overset{*}{C}H_2{-}N^+H_3}$$

With this method it is possible to determine the activity of the methylene carbon atoms[6] without interference from any amount of carboxyl carbon activity.

Malic acid has been oxidized with chromic acid to yield two molecules of carbon dioxide from the carboxyl groups and one molecule of acetic acid from the alpha and beta carbon atoms.

$$\mathrm{HOOC{-}\overset{*}{C}H_2{-}\overset{**}{C}HOH{-}COOH} \xrightarrow{\mathrm{CrO_3}} 2\mathrm{CO_2} + \mathrm{\overset{*}{C}H_3{-}\overset{**}{C}OOH}$$

The same procedure has been used to determine radioactive carbon fixed in the alpha and beta carbon atoms of aspartic acid. Degradation of the acetic acid may then be performed by decarboxylation.[7]

Experimental

Ethylenediurethan.—A tracer amount of unequally C^{14}-labeled succinic acid synthesized in the dark by preilluminated *Chlorella* was diluted by crystallizing with 300 mg. of succinic acid. The 280 mg. yield of crystalline acid was converted to methyl succinate in the usual manner with diazomethane and distilled quantitatively into a conical reaction flask. The hydrazide was prepared from the ester in 90% yield and was converted to the diurethan using the methods of Shöfer and Schwan[5] and Curtius.[4] The product was recrystallized from water and sublimed *in vacuo* to give a yield of 117 mg. (36%). The specific activity of a thin (less than 0.2 mg./sq.cm.) sample was determined with a Geiger counter and found to be 21.7 ± 1 c./m./mg.

Hydrolysis of Ethylenediurethan.—In a 30-ml. two-neck flask equipped with a reflux condenser and nitrogen inlet tube was refluxed a solution of 104 mg. of ethylenediurethan in 5 ml. of 48% hydrobromic acid for two hours. A slow stream of nitrogen gas during this period carried the evolved carbon dioxide through the condenser into a sodium hydroxide bubbler from which it was recovered as barium carbonate, 210 mg., specific activity 10.0 c./m./mg. The ethylenediamine was obtained upon evaporating excess acid *in vacuo* and adding excess methanolic potassium hydroxide. After evaporating the methanol, ethylenediamine was distilled *in vacuo* and converted to the dihydrochloride, 52 mg. (theoretical yield 68 mg.) by addition of methanolic hydrogen chloride. After recrystallization from methanol–water, the specific activity of the pure ethyl-

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[1] Calvin and Benson, *Science*, **105**, 648 (1947); **107**, 476 (1948).

[1a] This paper is based on work performed under contract No. W-7405-Eng-48 with the Atomic Energy Commission in connection with the Radiation Laboratory, University of California, Berkeley, California.

[2] Wood, Werkman, Hemingway and Nier, *J. Biol. Chem.*, **135**, 7890 (1940).

[3] Isherwood, *Biochem. J.*, **40**, 688 (1946).

[4] Curtius, *J. prakt. Chem.*, [2] **52**, 222 (1895).

[5] Shöfer and Schwan, *J. prakt. Chem.*, [2] **51**, 190 (1895).

[6] An activity of one count per minute determined on a 1 mg. sample of ethylenediamine dihydrochloride by the Nucleometer corresponds to 0.89 c./m./mg. or $8 \cdot 10^{-10}$ millicurie/mg. for the succinic acid.

[7] Aronoff, Haas and Fries, private communication.