Reactions of Dimethyl Sulfoxide with Sulfonate Esters of Fatty Alcohols. I. Synthesis of Higher Saturated and Unsaturated Fatty Aldehydes[1]

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ABSTRACT

Long-chain saturated fatty aldehydes (C_{10} to C_{18}), as well as the C_{18} unsaturated aldehydes (oleyl, linoleyl, and linolenyl), were synthesized in good yields by the selective oxidation of the sulfonate esters of the corresponding alcohols with dimethyl sulfoxide in the presence of sodium bicarbonate. Chromatographic procedures for the isolation of the pure aldehydes from the reaction mixtures are described. The purity of the aldehydes was ascertained by thin-layer chromatography, melting points of their 2,4-dinitrophenyl hydrazones, infrared spectra and other physical methods.

INTRODUCTION

STUDIES INVOLVING the isolation of aldehydes from the aldehydogenic lipids of various tissues and their characterization by gas-liquid chromatography necessitated the preparation of several fatty aldehydes to serve as standards.

Generally the aldehydes are prepared from the corresponding carboxylic acids via a derivative which is subsequently reduced (1). However, the available methods are usually either not suitable for the synthesis of aliphatic aldehydes or, alternatively, are restricted to saturated aliphatic aldehydes. Unsaturated aliphatic aldehydes are generally synthesized by Grundmann's method (2) or by the acyloin condensation reaction (3). In the former, an acid chloride is converted to the acetoxy ketone via the diazoketone. The glycol obtained by reduction of the keto group and simultaneous hydrolysis is cleaved by lead tetraacetate to yield the aldehydes containing the same number of carbon atoms as the starting material. By employing suitable modifications of this method, Mangold (4) prepared unsaturated fatty aldehydes in yields of approximately 30%. In the acyloin condensation method, the glycols are produced by reduction of the acyloins and cleaved by lead tetraacetate. Gauglitz and Malins (3) prepared polyunsaturated fatty aldehydes from fish oil fatty acids by this procedure. Although these two methods yield pure aldehydes, they involve a number of steps and the yields are rather low.

An alternative route for the synthesis of long-chain fatty aldehydes lies in the controlled oxidation of the corresponding alcohols. The reagents often used to oxidize alcohols to aldehydes are: chromium ion in sulfuric acid or pyridine (5); manganese dioxide (6); aluminum isopropoxide in acetone (7); and lead tetraacetate (8). The application of these reagents for the selective oxidation of long-chain fatty alcohols, especially the polyunsaturated ones, needs further investigation.

The use of dimethyl sulfoxide as a solvent and oxidizing reagent has steadily increased since it became commercially available. In 1959, Kornblum, Jones and Anderson (9) reported a simple procedure for the selective oxidation of benzylic tosylates and a short-chain alkyl tosylate to aldehydes in yields of 75% by dimethyl sulfoxide. The use of this reagent for the synthesis of oleyl and elaidyl aldehydes by oxidation of the corresponding tosylates was recently reported from this laboratory (10).

This paper describes the synthesis of long-chain saturated and polyunsaturated fatty aldehydes by oxidation of the tosylates and mesylates of the corresponding long-chain alcohols. Thin-layer chromatography (TLC) of the crude aldehydes revealed the presence of two minor by-products. One of them was identified as the α-olefin with the same number of carbon atoms as the alcohol. Methods for the isolation of the aldehydes from the oxidation mixture are described.

EXPERIMENTAL

Materials

The methyl esters of saturated fatty acids (>99% pure) were obtained from The Hormel Institute inventory of fatty acid derivatives and reduced with $LiAlH_4$ to the corresponding alcohols (11). Oleyl, linoleyl and linolenyl alcohols (>99% pure) were also obtained from this source. Dimethyl sulfoxide was obtained

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from a commercial source (Matheson, Coleman and Bell) and used without purification.

Preparation of Tosylates and Mesylates

The alcohols were converted to the tosylates with *p*-toluenesulfonyl chloride in pyridine by Tipson's method (12), and to the mesylates with methanesulfonyl chloride in pyridine as described by Baumann and Mangold (13). The purities of the tosylates and mesylates were checked by ascending thin-layer adsorption chromatography on Silica Gel G; they were found to be free from alcohols. The plates were developed with petroleum ether-diethyl ether (90:10, v/v) for tosylates and with petroleum ether-diethyl ether (70:30, v/v) for mesylates.

Oxidation of Tosylates and Mesylates by Dimethyl Sulfoxide

The oxidation of the tosylates and mesylates was accomplished by heating them with a mixture of sodium bicarbonate and dimethyl sulfoxide at 160C for 5–10 min. Efforts to produce the aldehydes by the same reaction at room temperature for 24 hr or by using dimethyl sulfoxide-acetic anhydride mixture as recently reported (14) were unsuccessful. The oxidations of palmityl tosylate and mesylate are selected for detailed description below, because the identification of one of the by-products, 1-hexadecene, in this case, rather than the unsaturated hydrocarbon from the corresponding unsaturated alcohols, was relatively easy.

In a 100 ml round-bottom ground-neck flask fitted with a condenser was placed 2.1 g palmityl tosylate, 1.0 g sodium bicarbonate and 10 ml dimethyl sulfoxide. Nitrogen was kept bubbling through the reaction mixture. The flask was immersed in a bath preheated at 165–170C. A vigorous reaction started in 1 min. After 5–10 min the reaction mixture was cooled rapidly to room temperature and poured into ice water. The precipitated material was extracted with ethyl ether, and the ether extract was washed once with oxygen-free water, dried over anhydrous Na_2SO_4 and filtered. All operations were conducted in a nitrogen atmosphere. Yield of crude palmityl aldehyde, 1.02 g.

Palmityl mesylate (2.27 g) on oxidation by the same procedure yielded 1.3 g of crude palmityl aldehyde.

Figure 1 shows the thin-layer chromatogram of the products of oxidation of palmityl tosylate and mesylate on Silica Gel G. The plate was developed with petroleum ether-ethyl ether (90:10, v/v) and the spots were made visible by spraying with 50% sulfuric acid and subsequent charring. In addition to the main oxidation product, palmityl aldehyde, two other reaction products obtained in minor quantities were also seen in each case. Small amounts of the starting material, as well as palmityl alcohol, were also present as impurities.

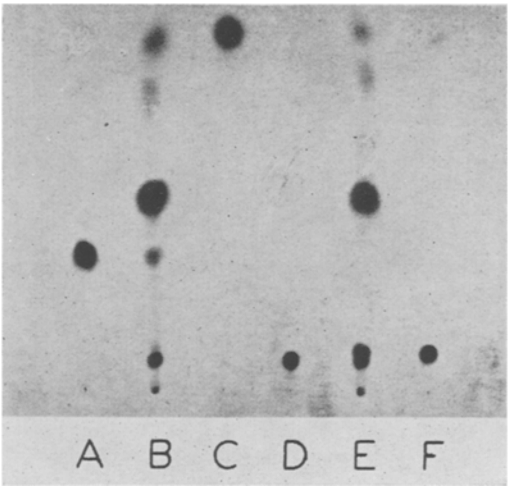


FIG. 1. Thin-layer chromatogram of oxidation products of palmityl tosylate and mesylate and reference compounds. Samples were: A) palmityl tosylate; B) oxidation products of palmityl tosylate (top to bottom; 1-hexadecene, unidentified compound, palmityl aldehyde, -tosylate and -alcohol); C) 1-hexadecene; D) palmityl alcohol; E) oxidation products of palmityl mesylate (top to bottom; 1-hexadecene, unidentified compound, palmityl aldehyde, -mesylate and -alcohol); F) palmityl mesylate.

Isolation of the Aldehyde as 2,4-Dinitrophenylhydrazone

The 2,4-dinitrophenylhydrazone of palmityl aldehyde was obtained from the reaction mixture (1.02 g) as described by Johnson (15) and recrystallized from 95% ethanol. Yield, 1.75 g.

Isolation of the Aldehyde by Column Chromatography

There is a large difference in distance of travel on the plate between the mesylate and the aldehyde. The difference in migration rates of the tosylate and the aldehyde is smaller than that of the mesylate and the aldehyde. This was also found to be the case with the system Silica Gel G/benzene. This indicated that the free aldehyde might be obtained pure by column chromatography if the mesylate rather than the tosylate were used as the starting material, and such was found to be the case.

The reaction product (1.3 g) was crystallized from 50 ml of petroleum ether (bp 30–60C) at −10C. This procedure removed the minor oxidation products. The unreacted mesylate and the alcohol could not be removed by crystallization techniques. However, they could be removed by a simple column chromatographic procedure. Silicic acid (Mallinckrodt, 100 mesh, chromatographic grade) was prepared for chromatography as described by Hirsch and Ahrens (16) without grinding the commercial product. Twenty grams of silicic acid was made into a slurry with petroleum ether (bp 30–60C), poured into a water-jacketed column (250 × 18 mm) and settled by frequent tapping. Nitrogen was kept bubbling through the slurry when the column was being prepared. Dissolved oxygen was removed from solvents by bubbling with nitrogen. The crude aldehyde (0.5 g) was dissolved in 5 ml of petroleum ether (bp 30–60C), applied on the column and washed with another 5 ml of the solvent. The solution was allowed to flow in without pressure until the liquid had been completely adsorbed. The aldehyde was then eluted with 250 ml of petroleum ether containing 5% diethyl ether. Most of the palmityl aldehyde appeared in this fraction and was recovered by evaporation of the solvents. The eluant can also be collected in 10 ml fractions and each fraction monitored for the presence of impurities by TLC. Alternatively, the aldehyde could be eluted from the column by benzene alone; 0.32 g of the crude aldehyde in benzene solution was applied on top of the column and the column was eluted with 300 ml of benzene. Evaporation of the solvent yielded 0.23 g of pure aldehyde. Further prolonged passage of benzene eluted the mesylate and the alcohol.

The yields and physical properties of the aldehydes and their 2,4-dinitrophenyl hydrazones are listed in Table I.

Identification of By-Products

The minor oxidation by-products obtained from both the tosylate and the mesylate seen in Figure 1 were isolated by preparative TLC. Chromatoplates, 8 × 8 in., were coated with 0.5 mm layers of Silica Gel G, which was repeatedly extracted with ethyl ether to remove any impurities. A solution of 100 mg of the crude reaction product in hexane was applied along a straight line about 1 cm from the edge of each plate and the plate was developed with petroleum ether-ethyl ether (90:10, v/v) for 45 min. The relevant portions of the adsorbent containing the impurities were scraped off the chromatoplate and were extracted with ethyl ether. Another plate was developed without any sample and a patch of the adsorbent equal in area to that of the sample was extracted to serve as a blank. The substances were recovered by evaporation of the ether in amounts of approximately 2% each of the crude aldehyde.

One of the by-products was identified as 1-hexadecene on TLC by comparison with a known standard. The material was also identified as 1-hexadecene by GLC using a Beckman GC-4 apparatus equipped with a hydrogen flame detector and a 6 ft column, $\frac{1}{8}$ in. O.D., containing 20% EGS on 80–100 mesh Gas-Chrom P by correlating retention time data for a standard sample of 1-hexadecene. The identity of the olefin was further substantiated by oxidizing it with the permanganate-periodate reagent of Von Rudloff (17). The expected oxidation product, n-pentadecanoic acid, was recovered and methylated with methanolic HCl and the methyl ester identified by GLC. The remaining oxidation by-product could not be identified with certainty.

Purity of the Aldehydes

The purity of the aldehydes was ascertained by TLC, melting points of their 2,4-

TABLE I

Yields and Melting Point of Aldehydes and 2,4-Dinitrophenyl Hydrazones (DNPH'S)

	% Yield of		MP. C[a] of DNPH	
Starting material	DNPH	Aldehyde	Observed	Literature (Ref.)
Decanol	61	63	104 – 105	104.2–104.8 (23) 108 (24)
Lauryl alcohol	65	62	105 – 106	105 –105.6 (23)
Myristyl alcohol	66	65	106.5–107.5	108.5–109 (23) 108 (24)
Palmityl alcohol	68	65	107 – 108	108 (24,25)
Stearyl alcohol	70	67	108 – 109	110 (24)
Oleyl alcohol	64	69	66 – 67	68 (24) 65.5– 66.5 (4)
Elaidyl alcohol	72	68	92.5– 93.5	90 (2)
Linoleyl alcohol	62	64	50 – 51	42.5– 43 (4)
Linolenyl alcohol	60	63	42 – 43	40.0– 40.5 (4)

[a] Melting points uncorrected.

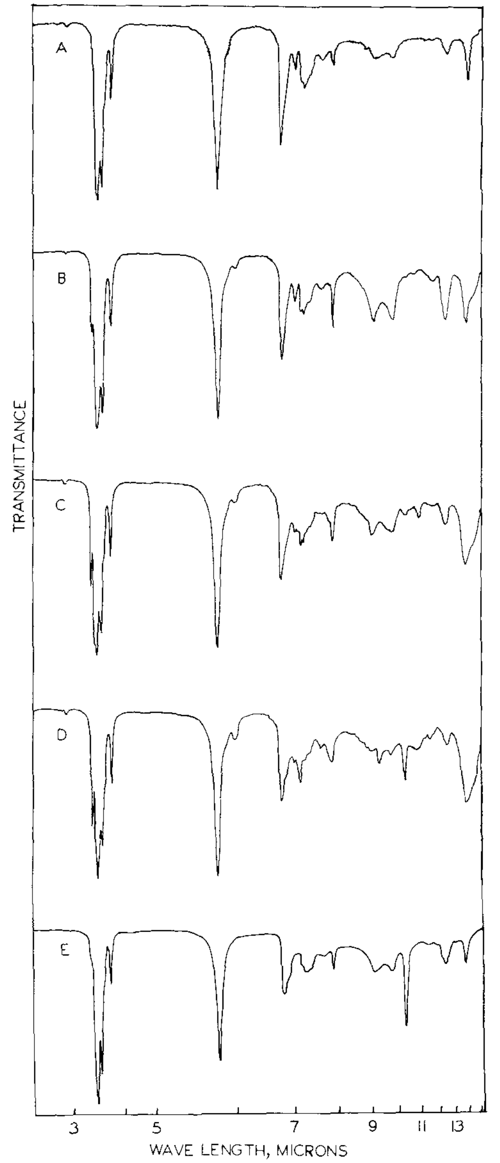


Fig. 2. Infrared spectra of fatty aldehydes. A) Stearaldehyde; B) oleyl aldehyde; C) linoleyl aldehyde; D) linolenyl aldehyde; E) elaidyl aldehyde. Solution spectra in 0.1 mm cell using 10% solutions of A-D and 8% solution of E in CS_2 (2.0 to 4.2 μ, 5 to 6.1 μ and 7.2 to 15.0 μ) and in tetrachloroethylene (4.2 to 5.0 μ and 6.1 to 7.2 μ).

dinitrophenylhydrazones (Table I), IR spectra and other physical methods. The purified aldehydes yielded single spots when analyzed by TLC using Silica Gel G/petroleum ether-ethyl ether (90:10, v/v) system. The aldehydes were also recovered from the plates and characterized as their 2,4-dinitrophenyl hydrazones.

Figure 2 shows the IR spectra of the pure aldehydes in CS_2 and C_2Cl_4 solutions between 2 and 15 μ. Bands characteristic of the aldehyde groups, 3.7 μ (2700 cm^{-1}) and 5.78 μ (1730 cm^{-1}) are present in all of the IR spectra. Bands characteristic of *cis* double bonds, 3.3 μ (3030 cm^{-1}) and 6 μ (1667 cm^{-1}) are seen in the spectra of oleyl, linoleyl and linolenyl aldehydes. No *cis* to *trans* isomerization occurred in the preparation of oleyl and linoleyl aldehydes. Linolenyl alcohol contained 10–15% of its unsaturation in the *trans* form. The same amount of *trans* unsaturation is found in the linolenyl aldehyde. Elaidyl aldehyde exhibited a strong absorption band at 10.3 μ (970 cm^{-1}).

TLC did not reveal the presence of any corresponding acids in the aldehydes. UV spectroscopy showed no conjugation in the linoleyl and linolenyl aldehydes. The purity of the aldehydes was also established by GLC. A Beckman GC-2A gas chromatograph equipped with a hydrogen flame detector and 12 ft aluminum column, 0.25 in. O.D., packed with Gas-Chrom R 30–60 mesh, and coated with 20% β-cyclodextrin acetate was used for the analysis. Temperature of the column was 230C and helium was the carrier gas. Each aldehyde exhibited a single peak when analyzed gas chromatographically. Figure 3 shows their separation when a hexane solution of the mixture was injected. Studies on the behavior of the aldehydes and their dimethyl acetals on stationary liquid phases commonly used in the GLC of fatty acid methyl esters are in progress.

Discussion

No satisfactory and universally applicable method has been described in the literature for the oxidation of long-chain saturated and unsaturated fatty alcohols to the corresponding aldehydes. These aldehydes are generally

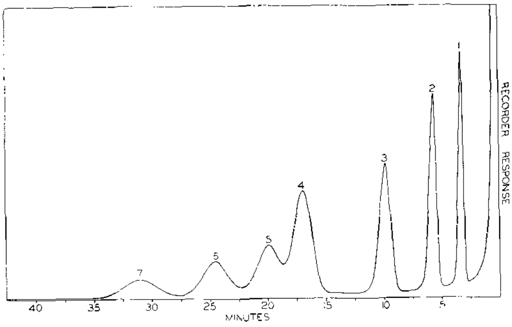
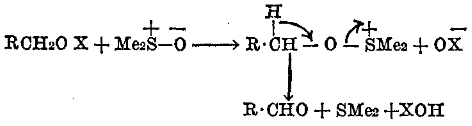


Fig. 3. GLC separation of fatty aldehydes. For experimental details, see text. 1) lauryl-; 2) myristyl; 3) palmityl-; 4) stearyl-; 5) oleyl; 6) linoleyl; 7) linolenyl-aldehyde.

synthesized from the derivatives of carboxylic acids and the synthesis involves a number of steps. The selective oxidation of the tosylates and mesylates of long-chain fatty alcohols by dimethyl sulfoxide has greatly facilitated the preparation of polyunsaturated fatty aldehydes in good yield. Under the conditions described, this reagent does not attack the double bond oxidatively nor cause any conjugation or *cis, trans* isomerization, unlike other reagents often used to oxidize alcohols to aldehydes.

The main product of the oxidation, the aldehyde, may be isolated as the 2,4-dinitrophenylhydrazine derivative if the free aldehyde is not immediately desired and converted directly to the dimethyl acetal as described by Mahadevan et al. (18) or to the free aldehyde by the method of Keeney (19) and Schogt et al. (20). However, the free aldehyde may also be obtained pure by a simple chromatographic procedure.

The mechanism suggested for this reaction (21) involves initial nucleophilic attack by dimethyl sulfoxide followed by collapse of the intermediate to aldehyde and dimethyl sulfide as shown below:



$$RCH_2OX + Me_2\overset{+}{S}-\overset{-}{O} \longrightarrow R\cdot\overset{H}{C}H-O-\overset{+}{S}Me_2 + \overset{-}{OX}$$
$$\downarrow$$
$$R\cdot CHO + SMe_2 + XOH$$

($X = p{-}C_6H_4Me\cdot SO_2$ or $CH_3\cdot SO_2$)

In the above reaction involving primary alkyl tosylates, elimination reactions giving rise to olefins have not been reported. On the other hand, with the sulfonic esters of secondary alcohols, olefins are formed readily under the same conditions (22). Generally the products of oxidation of primary alcohol sulfonates are isolated as their 2,4-dinitrophenylhydrazones and little effort has been made to detect the presence of olefins during the reaction. We have found that although aldehydes are the major products of the above reaction, olefin formation also does occur albeit to a small extent (2%). This observation has been made possible by the application of newer sensitive techniques of TLC and GLC. Although the sulfonate esters used as starting materials were free of alcohols, alcohols invariably were one of the minor products from the reactions. They might arise from the anhydrous reaction mixtures or by hydrolysis of some intermediate species during working up.

The reactions of dimethyl sulfoxide with long-chain alkyl halides and the sulfonate esters of hydroxy fatty acids under various experimental conditions are being investigated, which might hold great promise in the field of synthetic lipid chemistry.

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