

sample of trimethyl hemimellitate the melting point was 99–100.5°.

Characterization of III. A suspension of 28.4 g. (0.116 mole) of III in a solution of 5.2 g. (0.13 mole) of sodium hydroxide in 200 cc. of water was slowly heated until dissolved (at 65°) and the nitrile began to separate (at 72°). The nitrile was extracted with petroleum ether. To the water layer was added 1.3 g. of sodium hydroxide and the heating process was repeated twice until no more nitrile separated. Yield 10 g. (61%). This nitrile (5.5 g.) was refluxed 10 hr. with a mixture of 2.25 g. of potassium hydroxide, 3.5 cc. of water and 25 cc. of alcohol to give 3 g. of the known 2,4-dimethylphenylacetamide and 3.1 g. of the known 2,4-dimethylphenylacetic acid (see *f* in Table). The acid was smoothly oxidized by alkaline permanganate to trimellitic acid, m.p. 226–227°, lit.⁶ 228°.

III was further characterized by acidification of the ice-cold aqueous layer from the nitrile to yield 8.8 g. of shiny crystals. This product was dissolved in the minimum amount of hot 5% sodium hydroxide solution and reprecipitated by hydrochloric acid to give 6.5 g., m.p. 163–165°. It was

(6) Huntress and Mulliken, *Identification of Pure Organic Compounds I*, 116, 120 (1941). John Wiley and Sons, New York.

necessary to dry the product in vacuo as the crystals underwent slow decomposition in the air.

Anal. Calcd. for $C_{11}H_{12}O_3$: Neut. equiv., 192; C, 68.71; H, 6.29. Found: Neut. equiv., 194; C, 68.50; H, 6.38.

The acid reacted readily with Tollen's reagent to produce a silver mirror. It also gave a 2,4-dinitrophenylhydrazone, m.p. 201–202°. One attempt to oxidize the substance with permanganate to another crystalline acid gave only a viscous oil. The acid by-product was not further investigated.

Anal. Calcd. for $C_{17}H_{16}O_8N_4$: N, 15.05. Found: N, 15.06.

Characterization of IV. A mixture of 2.7 g. (0.11 mole) of IV, 6.0 g. (0.11 mole) of potassium hydroxide, 30 cc. of water and 45 cc. of alcohol was refluxed for 48 hr. The alcohol was distilled and water was added to precipitate the amide which was crystallized from hot alcohol. The aqueous filtrate was acidified to give 1 g. of crude acid. This sample of acid was oxidized with an excess of aqueous permanganate with stirring under reflux for 12 hr. The excess permanganate was destroyed by addition of a few drops of methanol. The hot aqueous filtrate was concentrated to a small volume, filtered, acidified, and extracted with ether to give 0.2 g. hemimellitic acid, m.p. 186–188°, lit.⁶ m.p. 190°.

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[CONTRIBUTION FROM THE HORMEL INSTITUTE, UNIVERSITY OF MINNESOTA]

Syntheses of Unsaturated Fatty Aldehydes¹

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Oleyl-, linoleyl- and linolenyl-aldehydes were prepared by a modified Grundmann synthesis. The procedure can be used for the preparation of radioactive aldehydes on a milligram scale.

Most methods reported² for the synthesis of aldehydes are not applicable to the preparation of aliphatic aldehydes having methylene-interrupted systems of double bonds. In the present investigation, the procedures described by Brown and McFarlin,³ Weygand,⁴ and Grundmann⁵ were selected as the most promising, and were compared by applying them to the synthesis of oleyl aldehyde. A modified Grundmann synthesis gave the purest

product and satisfactory yields and therefore it is described in detail.

Grundmann treated the acid chloride with diazomethane to obtain a diazo ketone, which was converted with acetic acid into a ketol acetate. The latter, after reduction with aluminum isopropylate and subsequent saponification, yielded a diol which was split with lead tetraacetate to give the aldehyde of the same chain length as the initial acid.

In the case of highly unsaturated compounds, the use of aluminum isopropylate results in the formation of polymers and the yields of diols are very low. The present author used lithium aluminum hydride for the reduction of ketol acetates² to avoid excessive condensations. It is not necessary to purify the ketol acetates since lithium aluminum hydride reduces the expected contaminants such as acid, acid chloride, ester, and chloroketone to mono alcohols which can be separated from the glycol by distillation or by column chromatography. Prolonged treatment of the diol with lead tetraacetate in the final reaction produces a small amount of contaminating acid, which can be extracted easily with dilute sodium carbonate solution. Neutral compounds, which appear as

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(2) E. Mosettig, "The Synthesis of Aldehydes from Carboxylic Acids," in *Organic Reactions*, John Wiley & Sons, Inc., New York, 1954, Vol. VIII, Chapter 5, p. 218; O. Bayer, "Methoden zur Darstellung und Umwandlung von Aldehyden," in *Methoden der Organischen Chemie*, Thieme-Verlag, Stuttgart, 1954, Vol. 7, 1, p. 1.

The use of lithium aluminum hydride as reducing agent in the Grundmann synthesis was already suggested by Mosettig.

(3) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **78**, 252 (1956).

(4) F. Weygand, *Angew. Chem.*, **65**, 525 (1953); S. S. Nigam and B. C. L. Weedon, *J. Chem. Soc.*, 3320 (1957).

(5) Chr. Grundmann, *Ann.*, **524**, 31 (1936).

contaminants in syntheses where a reduction is the final step, are very difficult to remove.

Radioactive oleyl aldehyde for metabolic studies was prepared from randomly-labeled oleic acid,⁶ all steps being carried out in a single test tube. The yield and purity of radioactive aldehyde were equal to those of "cold" preparations, despite its preparation on a micro scale. Each reaction product and purification procedure was checked by paper chromatography.⁷ By this means, formation of side products, yields, and purities could be determined without analytical difficulty or significant loss of material.

Infrared and ultraviolet spectra of the polyunsaturated aldehydes indicated that no steric changes of the system of double bonds occurred in the course of their synthesis.

EXPERIMENTAL

Oleic, linoleic, and linolenic acids were obtained from The Hormel Foundation.

All procedures were carried out under purified nitrogen, using oxygen-free water and anhydrous solvents free from peroxides. In all cases, the fatty acid chlorides were prepared from the acids by boiling for 2 hr. under reflux with a threefold excess of oxalyl chloride.⁸ This excess was removed at 80–90° under vacuum, and the residual fatty acid chlorides were used without further purification.

Fatty aldehydes via diazo ketones. The preparation of oleyl aldehyde will be given here. All other syntheses were performed under the same conditions.

(a) *Preparation of glycols.* Thirty grams (0.1 mole) of oleoyl chloride, dissolved in 100 ml. of ether, was added during a period of 10 min. to a stirred solution of 0.25 mole diazomethane in 500 ml. of ether kept at 0–5°. After warming to room temperature and standing for 2–4 hr., the excess diazomethane and most of the solvent were removed by a stream of nitrogen. The remaining yellow oil was added slowly to 50 ml. of acetic acid at 50–60°. After 2 hr. at this temperature the decomposition of the diazo ketone was completed by refluxing for 10 min.

The slightly yellow solution was poured into water and the ketol acetate was extracted with ether. The product was washed with water to neutrality and then dried over sodium sulfate. The ether was removed, first by evaporation and finally by heating the residual oil to 50° under high vacuum. The crude ketol acetate contained about 10% of chloro-ketone. Paper chromatography showed that the addition of potassium acetate, as suggested by Grundmann, does not improve the purity of the ketol acetate.

The crude ketol acetate in 200 ml. of ether was treated with an unfiltered solution of 4.0 g. (0.1 mole) of lithium aluminum hydride in 350 ml. of the same solvent. The sequence in which the reactants were added did not affect the quality and yield of the product. The mixture was refluxed for 1 hr. and, after addition of a little ethyl acetate, it was poured over 200 g. of crushed ice. The milky suspension was acidified with dilute sulfuric acid and extracted several times with ether. The product can be checked for complete reduction by warming a few milligrams with

several drops of 50% aqueous potassium hydroxide in a water bath.⁹ Residual ketol is indicated by a yellow or brown color. Paper chromatography indicated that these crude preparations contained about 10–15% of primary C₁₈ alcohol and about 5% of secondary C₁₉ alcohol and/or free acid. The mono alcohols and the glycols have boiling points of approximately 170° and 190–195° at 2 mm., respectively, and their separation by distillation is possible. A pear-shaped Claisen flask with a modified Pyros-Glover type receiver was used for this purpose. To keep the length of exposure to heat at a minimum, the products were distilled in portions of 0.1 mole or smaller from a bath preheated to 180°. Additional amounts of pure glycol were obtained by chromatographing the intermediate distilled fractions [6.5 g. in 15 ml. of petroleum ether (35–60°)] on alumina (40 g., activated, Harshaw) in a tube 2 × 30 cm. The chromatogram was developed successively with 100 ml. of methylene chloride, 100 ml. of ether, and 200 ml. of ethanol, a sequence of solvents which had been used by Trappe¹⁰ for similar fractionations. A total of 24 15-ml. fractions was collected, and each was spot-tested on paper.⁶ The first peak of the column chromatogram represented primary and secondary alcohols, which were not separated from each other, and about 1.5–2 g. of pure glycol was recovered from the second peak.

cis-Nonadecene-10-diol-1,2, m.p. 33.5–35.0°,¹¹ n_D^{20} 1.4583, was obtained in yields never below 15 g. (55%) in several experiments.

Anal. Calcd. for C₁₉H₃₈O₂: O, 10.75. Found: O, 10.4. Periodate titration: 100.5% glycol.

All-cis-nonadecadiene-10,13-diol-1,2, m.p. 17.5–19.0°, n_D^{40} 1.4720, was obtained in yields of about 45%, i.e., 12.5 g., from 28 g. of linoleic acid in several experiments.

Anal. Calcd. for C₁₉H₃₆O₂: O, 10.8. Found: O, 11.2. Periodate titration: 98.3% glycol.

All-cis-nonadecatriene-10,13,16-diol-1,2, m.p. 6.0–7.5°, n_D^{40} 1.4800, was obtained in yields of 10–12 g. (35–45%) when 28 g. of linolenic acid was used as starting material.

Anal. Calcd. for C₁₉H₃₄O₂: O, 10.9. Found: O, 11.2. Periodate titration: 98.4% glycol.

(b) *Preparation of aldehydes.* About 40–45 g. (0.1 mole) of lead tetraacetate and 0.5 ml. of acetic acid were added to a solution of 15 g. (0.05 mole) of nonadecene-10-diol-1,2 in 100 ml. of benzene and kept at 60° for 3 hr. Excess reagent was destroyed by addition of ethylene glycol. The solution was cooled to room temperature, poured into 500 ml. of 20% acetic acid in water, and extracted several times with benzene. The combined extracts were washed first with dilute acetic acid to remove the lead salts and finally with water to neutrality. Such preparations contain small amounts of free acids, which are removed by extracting the benzene solutions with 1% aqueous sodium carbonate. The aldehydes obtained in this manner are chromatographically pure. They are colorless and remain liquid at –20°. They may be distilled at 150–160°, 2 mm., and the analyses and yields reported refer to distilled products. The 2,4-dinitrophenylhydrazones were prepared in ethanol and sulfuric acid.¹²

Oleyl aldehyde, n_D^{20} 1.4538, was obtained in an amount of 9.0 g. (33% over-all yield) in the preparation described above.

Anal. Calcd. for C₁₈H₃₄O: C, 81.14; H, 12.86; O, 6.00. Found: C, 81.29; H, 12.40; O, 6.3.

2,4-Dinitrophenylhydrazone, yellow crystals from ethanol, m.p. 65.5–66.5° (reported m.p. 67–68°⁵).

(6) H. K. Mangold and H. Schlenk, *J. Biol. Chem.*, **229**, 731 (1957).

(7) H. K. Mangold, B. G. Lamp, and H. Schlenk, *J. Am. Chem. Soc.*, **77**, 6070 (1955); H. Schlenk, J. L. Gellerman, J. A. Tillotson, and H. K. Mangold, *J. Am. Oil Chemists' Soc.*, **34**, 377 (1957).

(8) T. R. Wood, F. L. Jackson, A. R. Baldwin, and H. E. Longenecker, *J. Am. Chem. Soc.*, **66**, 287 (1944).

(9) H. Schlenk, B. G. Lamp, and B. W. de Haas, *J. Am. Chem. Soc.*, **74**, 2550 (1952).

(10) W. Trappe, *Biochem. Z.*, **306**, 316 (1940); **307**, 97 (1941); *Hoppe-Seyler's Z. physiol. Chem.*, **273**, 177 (1942).

(11) All melting points are uncorrected.

(12) *Organic Reagents for Organic Analysis*, 2nd Edition, Hopkin & Williams, Ltd., Chadwell Heath, Essex, England, 1950, p. 68.

Linoleyl aldehyde, n_D^{20} 1.4632, was obtained in an amount of 7.5 g. (27%) using 28 g. of acid as starting material.

Anal. Calcd. for $C_{18}H_{32}O$: C, 81.76; H, 12.20; O, 6.05. Found: C, 81.45; H, 12.02; O, 6.6.

2,4-Dinitrophenylhydrazone, light orange crystals from ethanol, m.p. 42.5–43°.

Linolenyl aldehyde, n_D^{20} 1.4761, was obtained in several preparations in amounts of 6–6.5 g. (20–25%), using 28 g. of acid as starting material.

Anal. Calcd. for $C_{18}H_{30}O$: C, 82.39; H, 11.52; O, 6.1. Found: C, 82.11; H, 11.45; O, 7.19.

2,4-Dinitrophenylhydrazone, light orange crystals from ethanol, which decompose with darkening within 1 day at room temperature, m.p. 40–40.5°.

Paper chromatography. The paper chromatographic methods used to evaluate the synthetic procedures were essentially the same as described previously for other lipides.⁷ A system of 75% acetic acid in water with siliconized Whatman No. 1 paper at 30° was generally applied in the chromatography of starting materials and intermediates. The R_f values of oleyl, linoleyl, and linolenyl aldehydes were 0.15, 0.26, and 0.48, respectively. The diols were chromatographed with 60% aqueous tetrahydrofuran. Iodine vapors were used to locate the spots of unsaturated compounds on the paper.

Spectral analyses. According to their infrared spectra, oleic and linoleic acids were pure *cis* compounds, but linolenic acid, prepared by the bromination-debromination method, contained 5–10% of its unsaturation in *trans* form. The same amount of *trans* unsaturation was found in the triene-diol and in linolenyl aldehyde.

Absorption curves of the diols were obtained using carbon tetrachloride solutions in the near-infrared region (0.9–3 μ)¹³ and with carbon disulfide and tetrachloroethylene solutions between 2 and 15 μ . Only the bands characteristic of saturated and unsaturated hydrocarbon chains and of bounded O—H— groups were present. The aldehydes in the solvents mentioned also showed only bands characteristic of C—H— bonds, *cis* double bonds, and

aldehyde groups in the same regions. It was found that spectra of synthetic mixtures of a long-chain aldehyde with the corresponding acid do not reveal less than about 10% of the latter, under the conditions of measurement used. Considerably smaller percentages of acid can be detected by paper chromatography. No trimer¹⁴ was found in any of the aldehyde preparations by either infrared spectroscopy or paper chromatography, but they were detected in commercial samples of saturated aldehydes.

No conjugation was detected in any of the aldehydes by ultraviolet spectroscopy. When isomerized with alkali,¹⁵ maxima appeared at 232 $m\mu$ with linoleyl aldehyde or alcohol and at 232 and 268 $m\mu$ with the linolenyl analogs. The intensities of these absorptions were of the same magnitude as those obtained from linoleic and linolenic acids. The presence of such unsaponifiables, therefore, would give erroneous results when assaying the polyunsaturated fatty acids of biological materials by the alkali isomerization method.

After this paper was submitted for publication, the author became aware that the synthesis of unsaturated aldehydes by a Grundmann method was outlined, without experimental details, by H. P. Kaufmann.¹⁶

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(14) H. P. Kaufmann and H. Kirschnek, *Fette, Seifen, Anstrichmittel*, **55**, 847 (1953).

(15) R. T. Holman, in *Methods of Biochemical Analysis*, Interscience Publishers, Inc., New York, 1957, Vol. IV, pp. 99, 126.

(16) Meeting of the International Society of Industrial Chemists, Comunicaciones de las Secciones 13 A 23, Madrid, Oct. 22–31, 1955. Vol. II, p. 1085.

(13) R. T. Holman and P. R. Edmondson, *Anal. Chem.*, **28**, 1533 (1956).