

pyrimidines formed by condensation of acetophenone and phenylacetaldehyde with urea are reduced to the corresponding completely saturated cyclohexylhexahydropyrimidines, respectively.

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Branched Chain Aliphatic Acids. Isomyristic, Isopalmitic and Isostearic Acids

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The synthesis of higher aliphatic acids and their derivatives, of known constitution, is undertaken frequently for the purpose of establishing the structure of products isolated from natural sources. Since the conventional methods of extending carbon chains (involving the successive addition of increments of one or two carbons) are scarcely feasible for lengthening them by more than six atoms,¹ it is of advantage to employ a procedure in which a long chain can be added in a single operation. Two such methods have recently been developed: (a) the interaction of carbethoxy acyl chlorides, $\text{CO}_2\text{Et}-(\text{CH}_2)_n-\text{COCl}$, with sodium derivatives of substituted β -ketonic esters leading to ketonic acids of the type, $\text{CO}_2\text{Et}-(\text{CH}_2)_n-\text{CH}_2-\text{CO-R}$;² (b) the selective action of Grignard reagents upon aldehydic esters, $\text{CO}_2\text{Et}-(\text{CH}_2)_n-\text{CHO}$, to produce hydroxy acids such as $\text{CO}_2\text{H}-(\text{CH}_2)_n-\text{CHOH-R}$.³ In both instances the unsubstituted acids can be obtained by subsequent reduction of the ketonic or hydroxy acid.

In planning the synthesis of branched chain aliphatic acids containing the systems $(\text{CH}_3)_2\text{CH}-(\text{CH}_2)_n-\text{CO}_2\text{H}$ and $\text{CH}_3-\text{CH}_2-\text{CH}(\text{CH}_3)-(\text{CH}_2)_n-\text{CO}_2\text{H}$, an effort was made to devise a simpler method for adding large increments of carbon atoms. The fact that ketones can be obtained by the selective action of Grignard reagents upon simple acid chlorides⁴ suggested the use of the acid chlorides or acid chloride esters of dibasic acids to obtain ketonic acids of high molecular weight. Experiments using *n*-hexyl- and *n*-octylmagnesium bromides with sebacyl chloride gave the desired ketonic acids, 10-ketopalmitic and 10-ketostearic acids; although the yields in these reactions are relatively low (28 and 12% respectively),⁵ this is mitigated by the fact that ten carbon atoms are added in one simple operation.

(1) Levene and Allen, *J. Biol. Chem.*, **27**, 433 (1916); Levene and Taylor, *ibid.*, **59**, 905 (1924).

(2) (a) Robinson and Robinson, *J. Chem. Soc.*, **127**, 175 (1925); (b) 2204 (1926); (c) Robinson, *ibid.*, 745 (1930).

(3) Noller and Adams, *THIS JOURNAL*, **48**, 1074 (1926). Numerous applications of this method are described in subsequent papers by Adams and his collaborators.

(4) Cf. Nilanidhi, Dawson and Johnson, unpublished investigations. In this work succinic anhydride was used to effect an addition of four carbon atoms, giving a γ -ketonic acid.

(5) These yields are similar to those obtained (10–25%) in the synthesis of hydroxystearic acids by the aldehydic ester method [Tomecko and Adams, *THIS JOURNAL*, **49**, 522 (1927)].

Reduction of the ketonic acids by the method of Clemmensen⁶ gave the corresponding fatty acids in satisfactory yields.

For the synthesis of isopalmitic acid the requisite isohexyl alcohol was obtained by the action of ethylene oxide upon isobutylmagnesium bromide. Isoöctyl alcohol was prepared by a similar reaction from isohexylmagnesium bromide. Reaction of isohexyl- and isoöctylmagnesium bromides with sebacyl chloride produced 10-keto-isopalmitic and 10-keto-isostearic acids in yields of 24 and 11%, respectively. The reduction of these ketonic acids gave isopalmitic acid (m. p. 61.8–62.4°) and isostearic acid (m. p. 67.6–68.2°).

The synthesis of isomyristic acid was effected through 10-keto-isomyristic acid, obtained by the action of isobutylmagnesium bromide upon the acid chloride of the mono-ethyl ester of sebacic acid ($\text{CO}_2\text{Et}-(\text{CH}_2)_8-\text{COCl}$).⁷ This reagent was found to give more satisfactory yields (40–45%) than sebacyl chloride. Reduction of the ketonic acid gave isomyristic acid (m. p. 50.5–51.5°). The over-all yield in these preparations was 25–30% of the theoretical. Isomyristic acid was also prepared via the aldehydic ester method,⁸ using isoamylmagnesium bromide and methyl 8-aldehydo-octanoate. The resulting methyl 9-hydroxy-isomyristate was converted to the unsubstituted acid by the general procedure of Noller and Adams,³ and an over-all yield of 15–18% was obtained. This direct comparison indicates an advantage in favor of the acid chloride ester method; furthermore, the accessibility of a variety of dibasic acids ($\text{C}_5\text{--C}_{10}$ and C_{13}) gives the latter a somewhat broader scope.

Experimental

Sebacyl Chloride.—A mixture of 50 g. of sebacic acid and 75 g. of purified thionyl chloride was warmed at 50° for twelve hours and finally refluxed for one hour. After removal of the excess of thionyl chloride under reduced pressure there was obtained 50 g. (84%) of sebacyl chloride, b. p. 155–156° at 8 mm. It is advantageous to distil this substance rapidly, in quantities not above 50 g. in a single operation.

9-Carboethoxynonyl Chloride.⁹—To 50 g. of sebacyl chloride, 9.5 g. of absolute ethyl alcohol was added *very slowly* with efficient stirring. The mixture was warmed gently under reduced pressure and finally allowed to stand in a vacuum desiccator over potassium hydroxide. The residual product is sufficiently pure for synthetic work, but may be purified by distillation if necessary; b. p. 158–160° at 7 mm. On treatment with aniline, the undistilled product gave 9-carboethoxynonyl anilide, m. p. 60–61°.

10-Ketopalmitic Acid.—To a stirred solution of 31 g. (0.13 mole) of sebacyl chloride in 250 cc. of ether, a solution of 0.11 mole of *n*-hexylmagnesium bromide (0.5 molar) was added during one hour while the temperature was maintained at 25–26°. The mixture was stirred for one-half hour longer and was decomposed with iced acid. After

(6) Clemmensen, *Ber.*, **46**, 1841 (1913).

(7) Cf. Davies and Adams, *THIS JOURNAL*, **50**, 1754 (1928). Organozinc compounds have been used similarly in the preparation of ketonic acids;⁸ however, the use of zinc compounds has been limited to the lower primary alkyl groups [cf. Noller, *THIS JOURNAL*, **51**, 594 (1929)].

(8) Blaise, *Bull. soc. chim.*, [4] **9**, 1 (1911).

(9) This preparation and the synthesis of isomyristic acid from 9-carboethoxynonyl chloride were carried out by Dr. R. C. Tallman.

removal of the ether, the residue was treated with 1 liter of 5% potassium hydroxide; an alkali insoluble fraction was removed by filtration and washed with another small portion of alkali (see below). Upon pouring the alkaline solution into cold hydrochloric acid there was precipitated a mixture of 10-ketopalmitic and sebacyl acids. The mixed acids were redissolved in alkali and the ketonic acid was separated by careful fractional acidification, leaving the sebacyl acid in solution. The crude 10-ketopalmitic acid was reprecipitated from alkaline solution and was recrystallized twice from ethyl acetate. The yield of purified acid was 8.5 g. (28%); m. p. 75–75.8°, neut. equiv. 269.6, 267.0 (calcd. 270.2). When the reaction was carried out at 0°, the yield of the ketonic acid fell to 20%.

Anal. Calcd. for $C_{16}H_{30}O_3$: C, 71.06; H, 11.18. Found: C, 70.72, 70.85; H, 11.21, 11.16.

The semicarbazone of the acid, after recrystallization from alcohol, melted at 154–155°. Catalytic hydrogenation of the ketonic acid, in glacial acetic acid, gave 10-hydroxypalmitic acid; m. p. 65–66°. Reduction of the ketonic acid with a large excess of amalgamated zinc and hydrochloric acid gave palmitic acid (m. p. 61.6–62.2°) in 63% yield.

The alkali insoluble by-product of the original reaction (1.0 g.) was recrystallized from ether; m. p. 85.8–87°. A molecular weight determination by the method of Rast gave the value 348, indicating that the product was formed from the reaction of two molecules of hexylmagnesium bromide and one of sebacyl chloride (calcd. for $(C_6H_{13})_2$, 338; for $(C_6H_{13})_3$, 424). This compound might therefore be a diketone (7,16-diketodocosane) or the cyclic lactone of 10-hexyl-10-hydroxypalmitic acid. Attempts to form a semicarbazone or oxime of the substance were unsuccessful.

10-Ketostearic Acid.—Using *n*-octylmagnesium bromide in the procedure given above, there was obtained 4.0 g. (12% yield) of the ketonic acid. After two crystallizations from ethyl acetate the acid melted at 82–82.8°; neut. equiv. 301.4, 296.5 (calcd. 298.2). The melting point of 10-ketostearic acid obtained from 9-carbomethoxynonyl chloride and ethyl sodio-*n*-hexylacetoacetate^{2b} was reported as 82°.

Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.48; H, 11.45. Found: C, 72.45, 72.61; H, 11.66, 11.64.

The semicarbazone of 10-ketostearic acid melted at 121–122°.

10-Keto-isopalmitic Acid (14-Methyl-10-ketopentadecanoic Acid).—Isohexyl alcohol was prepared from isobutylmagnesium bromide and ethylene oxide¹⁰ in yields of 35–40%; b. p. 145–150° at 735 mm. The alcohol, on warming with hydrobromic-sulfuric acids, gave isohexyl bromide in 74% yield; b. p. 142–145° at 735 mm. The latter was converted to isohexylmagnesium bromide (90–92% yield) and this was allowed to react with sebacyl chloride, as described above. The yield of 10-keto-isopalmitic acid from 31 g. of sebacyl chloride and 0.11 mole of the Grignard reagent was 7.4 g. (24%). After two crystallizations from ethyl acetate the acid melted at 68–69°; neut. equiv. 271.8, 273.6 (calcd. 270.2). An attempt to obtain the semicarbazone of this acid was unsuccessful.

Anal. Calcd. for $C_{16}H_{30}O_3$: C, 71.06; H, 11.18. Found: C, 71.29, 70.79; H, 11.21, 11.27.

Isopalmitic Acid (14-Methylpentadecanoic Acid).—Four grams of the ketonic acid was refluxed gently with 50 g. of amalgamated zinc and 50 cc. of concd. hydrochloric acid for twelve hours, with stirring; during this period four additional 10-cc. portions of acid were introduced at intervals, as the reaction slackened. At the end of twelve hours the liquid organic acids were decanted from the warm mixture and the reduction process was repeated. The organic acid after decantation from the warm reaction mixture solidi-

(10) Cf. "Organic Syntheses," 1932, Coll. Vol. I, p. 299.

fied on cooling; it was purified by precipitation as the magnesium salt. There was obtained 3.0 g. of isopalmitic acid (79% yield); recrystallized from ethyl acetate, m. p. 61.8–62.4°, neut. equiv. 257.1, 257.0 (calcd. 256.3).

10-Keto-isostearic Acid (16-Methyl-10-ketoheptadecanoic Acid).—Isooctyl alcohol, b. p. 90–95° at 15 mm., was obtained from isohexylmagnesium bromide and ethylene oxide in 60–65% yield. The corresponding bromide, b. p. 65–68° at 10 mm., was converted into isooctylmagnesium bromide (75–78% yield), and the latter was allowed to react with 31 g. of sebacyl chloride in the manner described above. The alkaline solution of the crude organic acids was extracted with ethyl acetate to remove the neutral by-products and the ketonic acid was precipitated by fractional acidification. There was obtained 3.8 g. (11% yield) of 10-keto-isostearic acid, which, after two recrystallizations from ethyl acetate, melted at 71.2–72°; neut. equiv. 299.7, 297.7 (calcd. 298.2).

Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.48; H, 11.45. Found: C, 72.72, 72.29; H, 11.50, 11.50.

Isostearic Acid (16-Methylheptadecanoic Acid).—Two grams of the ketonic acid on reduction in the usual way gave 1.5 g. of isostearic acid (76% yield); m. p. 67.6–68.2°, neut. equiv. 284.9, 283.6 (calcd. 284.3).

10-Keto-isomyristic Acid (12-Methyl-10-ketotridecanoic Acid).⁹—Slightly less than the calculated quantity of isobutylmagnesium bromide was added dropwise, with stirring, to a solution of 24.9 g. (0.1 mole) of 9-carbethoxynonyl chloride in 50 cc. of ether. The reaction mixture was allowed to stand for twelve hours and was finally refluxed gently for one hour. The product was decomposed with iced acid and the crude ketonic ester was hydrolyzed by refluxing for four hours with alcoholic potassium hydroxide solution. The mixture of keto-isomyristic acid and sebacic acid was separated by fractional acidification of the alkaline solution, in the usual way. The yield of partly purified 10-keto-isomyristic acid, m. p. 52–53°, was 10.4–11.2 g. (43–47%). After two recrystallizations from petroleum benzene the acid melted at 54–55°; neut. equiv. 242.2 (calcd. 242.0).

A small quantity of alkali-insoluble material was separated after saponification of the crude ketonic ester. After two recrystallizations from alcohol the substance melted at 43–44°; molecular weight by the method of Rast, 277; semicarbazone derivative, m. p. 193–194°. This compound is probably similar to the alkali insoluble by-product obtained in the preparation of 10-ketopalmitic acid. It is apparently a diketone (2,15-dimethylhexadecane-4,13-dione, mol. wt. 282), arising from the presence of small amounts of sebacyl chloride in the 9-carbethoxynonyl chloride.

Isomyristic Acid (12-Methyltridecanoic Acid).—Twelve grams of 10-ketoisomyristic acid was reduced with two 50-g. portions of amalgamated zinc in the usual way. The reduced acid (60–65% yield) after recrystallization from ethylene dichloride and from petroleum ether, melted at 50.5–51°; neut. equiv. 228.2, 227.0 (calcd. 228.2).

Methyl 9-Hydroxy-isomyristate.¹¹—Synthetic isoamyl alcohol, from isopropylmagnesium bromide and ethylene oxide, was converted to isoamyl bromide (b. p. 119.5–120° at 745 mm.) and the latter was transformed into isoamylmagnesium bromide. A solution of this Grignard reagent (0.5 mole) was added dropwise to an ethereal solution of 95 g. (0.5 mole) of methyl 8-aldehydo-octanoate,³ at –10°. Repeated fractionation of the reaction product gave 72.5 g. (30% yield) of methyl 9-hydroxy-isomyristate; b. p. 146–153° at 1 mm., n_D^{20} 1.4470.

Oxidation with chromic oxide in acetic acid gave the corresponding ketonic ester, which was hydrolyzed to 9-keto-isomyristic acid, m. p. 58.2–59.5°.

(11) We are indebted to Mr. D. C. Maddy and Dr. Karl Folkers for a large part of the experimental work on this and the following preparation, carried out in the University of Illinois laboratories.

Isomyristic Acid.—The hydroxy-isomyristic ester from the preceding preparation was converted to the unsubstituted acid according to the method used by Noller and Adams for *n*-tridecanoic acid. The crude isomyristic acid was esterified by warming with ethyl alcohol (+H₂SO₄) and the resulting ester was carefully fractionated. The yield of purified ethyl isomyristate was 45–50% (based on the hydroxy ester); b. p. 140–142° at 5 mm., n_D^{20} 1.4342. Hydrolysis of the ester gave isomyristic acid, which after recrystallization melted at 50–50.5°. This acid showed no depression of the m. p. when mixed with that obtained from 10-keto-isomyristic acid.

Reduction of ethyl isomyristate with sodium and alcohol gave isomyristyl alcohol (75–80% yield); b. p. 145–150° at 6 mm., m. p. 10–11°, d_4^{20} 0.8429, n_D^{20} 1.4437. This alcohol on warming with a large excess of 48% hydrobromic acid (+H₂SO₄) gave isomyristyl bromide (80% yield); b. p. 120–122° at 3 mm., d_4^{20} 1.0241, n_D^{20} 1.4598.

Summary

The selective action of alkylmagnesium halides upon sebacyl chloride and 9-carbomethoxynonyl chloride has been used for the synthesis of straight and branched chain ketonic acids of high molecular weight (C₁₄–C₁₈). This reaction constitutes a simple method for the addition of ten atoms to a carbon chain.

Isomyristic, isopalmitic and isostearic acids were prepared by reduction of the corresponding ketonic acids.

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The Structure of α -Benzoyl α -Bromo Esters

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The unusual properties of those organic bromo compounds in which a bromine atom has replaced a hydrogen of an active methylene group have been recognized for some time. The fact that certain of these substances are hydrolyzed by sodium hydroxide solution into sodium hypobromite led the earlier investigators¹ to the view that such substances contained an oxygen to bromine linkage. This view was regarded as untenable by MacBeth² who, in the course of a study of certain members of this class, found that, while these substances oxidized hydrazine quantitatively to nitrogen, they gave absorption spectra characteristic of compounds having an ordinary carbon to halogen bond. In a more recent paper, which admirably reviews the literature of this class of compounds, Schmidt, Ascherl and von Knilling³ emphasize the similarity between the chemical behavior of this type of halide, which they term a persubstituted halogen compound, and the N-halogenated acylamines. They showed that persubstituted bro-

(1) Willstätter and Hottenroth, *Ber.*, **37**, 1776 (1904); Flatow, *ibid.*, **37**, 1787 (1904).

(2) MacBeth and Graham, *J. Chem. Soc.*, **121**, 1115 (1922).

(3) Schmidt, Ascherl and von Knilling, *Ber.*, **59**, 1876 (1926).