

SYNTHESES OF A SERIES OF 15-KETOGLYCOLS AND 15-KETO FATTY ACIDS FROM USTILIC ACID¹

By A. T. CROSSLEY² AND B. M. CRAIG

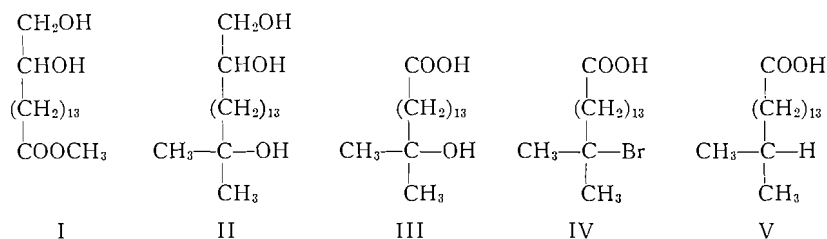
ABSTRACT

Reaction of the methyl ester of ustilic acid A (15,16-dihydroxypalmitic acid) with a methyl Grignard, oxidation of the glycol grouping, bromination, and hydrogenolysis produced 15-methylhexadecanoic acid. A series of 15-keto acids resulted from reaction of the amide of ustilic acid A with the appropriate Grignard reagent followed by oxidation of the glycol grouping. Infrared absorption characteristics of these compounds are described.

Ustilagic acid has been produced by fermentation using a culture of *Ustilago zea* (2). Ustilic acid A (15,16-dihydroxypalmitic acid) and ustilic acid B (2,15,16-trihydroxypalmitic acid) are produced by hydrolysis of ustilagic acid (4). These acids are easily separated from the remainder of the hydrolysis products and from one another and are potentially available in large quantities.

The ustilic acids possess a carboxyl group at one end of the molecule and an easily oxidizable glycol grouping at the other end and as such should constitute valuable starting materials for the synthesis of various new and naturally occurring long chain compounds. The present investigation deals with the synthesis of 15-methylhexadecanoic acid and a series of 15-keto acids.

A number of methyl branched fatty acids which are primarily concerned with the wool fats have been synthesized by a number of workers (1, 3, 7, 8, 9). These syntheses have involved the preparation of appropriate fragments followed by chemical coupling or anodic syntheses. Weitkamp (9) prepared 15-methylhexadecanoic acid from a lower homologue and Stenhagen *et al.* synthesized the same acid (1). Ustilic acid A is a convenient starting material for the synthesis of this acid by the following series of reactions:



Methyl ustilate A (I) was converted in almost theoretical yield into the tertiary alcohol II, m.p. 55.5–56.0° C., by using a large excess of methylmagnesium bromide. Reaction of methyl isopropylidene ustilate A with the Grignard reagent followed by removal of the isopropylidene grouping with

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methanolic hydrochloric acid gave a very poor yield of II. Oxidation of II with chromic oxide in acetic acid at low temperature gave 15-methyl-15-hydroxy-hexadecanoic acid III, m.p. 70.5–71.5° C., which yielded *p*-bromophenacyl derivative, m.p. 80.6–81.0° C. This oxidation was also carried out using lead tetraacetate and oxygen as described below. The hydroxy acid III was treated with hydrogen bromide in acetic acid to give the tertiary bromo derivative IV, m.p. 45–46° C., which, on treatment with hydrogen and Raney nickel in ethanolic sodium hydroxide, gave 15-methylhexadecanoic acid V, m.p. 60.7–61.3° C. (reported m.p. 59.3–59.9° C. (1) and 60.2° C. (9)).

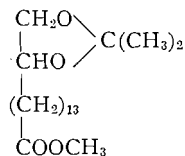
The synthesis of a series of 15-keto acids was carried out by the series of reactions given below. To favor the formation of the ketoglycol rather than the tertiary alcohol derivative, the amide of ustilic acid A was used as a starting material in the Grignard reaction. The reaction of amides with Grignard reagents has been investigated by Whitmore *et al.* (10, 11). To increase solubility the isopropylidene derivative (VII) was used. Reaction of the latter with 1.1 moles of methylmagnesium bromide gave a poor yield of the ketone (VIII) (R = CH₃), m.p. 40.0–41.0° C., semicarbazone m.p. 123.5–124.0° C., but the yield was increased by the use of 100% excess of the Grignard reagent. A small amount of the tertiary alcohol formed was separated on alumina. The corresponding ethyl, propyl, and butyl homologues (VIII) were also prepared by using the appropriate Grignard reagents. These had melting points, respectively, of 37° C. (R = C₂H₅), 43° C. (R = C₃H₇), and 48.5° C. (R = C₄H₉). Removal of the isopropylidene group afforded the free ketoglycols (IX) which are described in Table I. Purification of the latter compounds was greatly facilitated by a treatment with warm alcoholic alkali before crystallization from benzene.

TABLE I
MELTING POINTS AND ELEMENTAL ANALYSIS OF KETOGLYCOLS AND KETO ACIDS

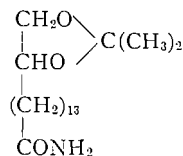
Compound	Formula	M.p., ° C.	Found		Calculated	
			C (%)	H (%)	C (%)	H (%)
1,2-Dihydroxy-16-ketoheptadecane	C ₁₇ H ₃₁ O ₃	83.0–83.7	71.34	12.07	71.28	11.96
1,2-Dihydroxy-16-ketooctadecane	C ₁₈ H ₃₆ O ₃	93.8	72.43	11.48	72.44	11.51
1,2-Dihydroxy-16-ketononadecane	C ₁₉ H ₃₈ O ₃	92.5	73.39	11.59	73.02	11.61
1,2-Dihydroxy-16-ketoeicosane	C ₂₀ H ₄₀ O ₃	93.9	73.08	12.07	73.11	12.27
15-Ketohexadecanoic acid*	C ₁₆ H ₃₀ O ₃	82.3	70.86	11.10	71.07	11.18
15-Ketoheptadecanoic acid	C ₁₇ H ₃₂ O ₃	85.7–86.1	71.73	11.44	71.78	11.34
15-Ketooctadecanoic acid	C ₁₈ H ₃₄ O ₃	83.4	72.44	11.51	72.43	11.48
15-Ketononadecanoic acid	C ₁₉ H ₃₆ O ₃	85.7	73.39	11.59	73.03	11.61

*Semicarbazone, m.p. 129.6° C. (C, 62.57; H, 10.22; N, 12.82%. Calc. for C₁₇H₃₃O₃N₃: C, 62.35; H, 10.16; N, 12.88%.)

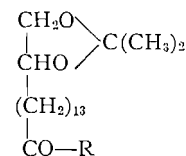
These ketoglycols (IX) were converted to 15-keto fatty acids (X) by simultaneous oxidation with lead tetraacetate and oxygen at 50° C. according to the method of Mendel and Coops (6). The oxidation products were purified by distillation and crystallization from alcohol. The melting points of these four, hitherto unprepared, keto fatty acids are given in Table I.



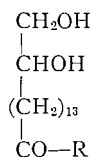
VI



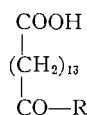
VII



VIII



IX



X

Infrared absorption determinations were made on all the compounds with a Perkin-Elmer Model 21 instrument equipped with a sodium chloride prism, and the crystalline samples were mounted in KBr. The 15-methyl-15-hydroxy-hexadecanoic acid showed OH absorption bands at 3440 and 1152 cm^{-1} , and also several poorly resolved bands between 1390 and 1300 cm^{-1} which might be caused by the $(\text{CH}_3)_2\text{C}-$ group. The 15-methylhexadecanoic acid showed two clearly resolved bands at 1385 and 1365 cm^{-1} which are characteristic for branched methyl groups. These bands were absent in the spectrum of pure hexadecanoic acid. The 1,2-dihydroxy-15-keto compounds showed the expected hydroxyl band between 3400 and 3200 cm^{-1} and also two absorption bands at 1100 and 1082 cm^{-1} which could be assigned to a secondary and a primary hydroxyl group respectively. They also showed the ketonic carbonyl absorption between 1710 and 1705 cm^{-1} . The corresponding 15-keto acids showed absorptions in the 1700 cm^{-1} and the 900-700 cm^{-1} regions characteristic for carboxylic acids. Resolutions of the carboxyl $\text{C}=\text{O}$ and ketone $\text{C}=\text{O}$ were achieved in the 1720-1700 cm^{-1} region for 15-ketohexadecanoic and 15-ketoheptadecanoic acids but not for 15-ketooctadecanoic and 15-ketononadecanoic acids. The $\text{C}=\text{O}$ absorption band in the latter was much wider than for the corresponding 15-keto-1,2-dihydroxy-nonadecane and -eicosane.

EXPERIMENTAL

NOTE: All melting points are corrected and determinations have been made in each case in the usual manner and also on a heating stage microscope.

Separation of the Ustilic Acids

A ustilic acid mixture (158 gm.), prepared by hydrolysis of ustilic acid (4), was shaken for four hours with 1 liter of dry acetone containing 1% sulphuric acid. A small amount of inorganic material remained insoluble and the solution was filtered into a separatory funnel containing 3 liters of ice-cold water. The solution was extracted with 1.6 liters of petroleum ether (b.p. 60-80° C.) and the mother liquor was extracted with a further 1 liter. The combined petroleum ether extracts were washed three times with water. A cold solution of 60 gm. of potassium hydroxide in 420 ml. of water was then added and after

one minute's shaking, 450 ml. of 40% aqueous ethanol was added and the aqueous layer run off. The petroleum ether extract was then washed with 500 ml. of 3% aqueous potassium hydroxide and three times with 30% aqueous ethanol. The five aqueous ethanol washings were combined and diluted with 1 liter of water and re-extracted with 400 ml. petroleum ether, the extract being added to the main bulk of petroleum ether solution. The aqueous extract was acidified with sulphuric acid and extracted with chloroform to yield 163 gm. of crude isopropylidene ustilic acid A which was recrystallized from acetone to m.p. 64–65° C. The petroleum extracts gave 12 gm. of diisopropylidene ustilate B, m.p. 42–43° C., reported m.p. 42.5–43° C. (5).

The proportions of the ustilic acids in the mixture have been found to vary slightly and the present mixture represents the highest proportion of ustilic acid A which has been found. The amount may fall to about 70% of the mixture of acids.

Methyl Isopropylidene Ustilate A

Isopropylidene ustilate A (154 gm.) was esterified with diazomethane in dry ether to yield 160 gm. of the crude product as outlined in the procedure of Lemieux (5). Two crystallizations from acetone at 4° C. gave the pure methyl ester, m.p. 46.3–46.7° C., reported m.p. 46–47° C. (5).

Methyl Ustilate A

Isopropylidene ustilic acid A (20 gm.) was boiled under reflux with 4% methanolic HCl for two hours as outlined by Lemieux (5). The solution was poured into water and extracted with chloroform to give 16.2 gm. of crude methyl ustilate A, which after three crystallizations from ethanol had m.p. 85.2–86.1° C., reported m.p. 85.5–86.0° C. (5).

1,2,16-Trihydroxy-16-methylheptadecane

Methyl ustilate A (10 gm.) in 200 ml. of dry ether was added during one hour, with rapid stirring, to 23.5 gm. of methylmagnesium iodide in 300 ml. of ether, the mixture being allowed to reflux continuously during the addition. The semisolid reaction mixture was boiled under reflux for 10 hr. and was then decomposed with water and acetic acid. The crude tertiary alcohol, 10.1 gm., m.p. 54.0–55.0° C., was extracted with chloroform. The 1,2,16-trihydroxy-16-methylheptadecane purified by one crystallization from acetone had a m.p. 55.5–56.0° C. Calc. for $C_{18}H_{38}O_3$: C, 71.50; H, 12.60%. Found: C, 71.33; H, 12.50%.

15-Hydroxy-15-methylhexadecanoic Acid

The above tertiary alcohol (5.0 gm.) was dissolved in 140 ml. of acetic acid containing 7.0 gm. of chromic oxide and the solution allowed to stand for 12 hr. at 3° C., when it was diluted with ice-cold water (1 liter) and extracted with benzene. The benzene solution was washed with water until neutral and the benzene evaporated. The crude hydroxy acid was then taken up in 100 ml. of ether and the ether washed twice with 5% aqueous potassium hydroxide, and twice with water. The combined washings were acidified with sulphuric acid and extracted with ether to yield 2.63 gm. of 15-hydroxy-15-methyl-

hexadecanoic acid, which was purified by three crystallizations from acetone and crystallized as colorless needles, m.p. 70.5–71.5° C. Calc. for $C_{17}H_{34}O_2$: C, 72.10; H, 11.95%. Found: C, 72.45%; H, 12.06%.

15-Bromo-15-methylhexadecanoic Acid

The hydroxy acid (1.39 gm.) was dissolved in 10 ml. of a 50% solution of hydrobromic acid in acetic acid and left for 14 hr. at 22° C. The solution was then diluted with 100 ml. of ice-cold water and the product extracted with benzene. Yield, 1.71 gm.; m.p. 45.0–46.5° C. Calc. for $C_{17}H_{33}O_2Br$: Br, 22.6%. Found: Br, 22.5%.

15-Methylhexadecanoic Acid

The 15-bromo-15-methylhexadecanoic acid (1.65 gm.) was dissolved in 25 ml. of ethanol, and 50 ml. of ethanol containing 5 ml. of 4 *N* sodium hydroxide added, together with a small amount of Raney nickel. The mixture was shaken with hydrogen under a pressure of 25 p.s.i. for 1½ hr. at 25° C. The solution was filtered, poured into dilute sulphuric acid, and the product extracted with ether. Unexpectedly this material contained a large proportion of unsaturated material (iodine value 40) and it was therefore hydrogenated, in a similar medium to that previously used, but at a temperature of 80° C. and a pressure of 800 p.s.i. of hydrogen, for four hours. The product was saturated (iodine value 0), and was purified by distillation followed by three crystallizations from ethanol. The pure 15-methylhexadecanoic acid had m.p. 60.7–61.3° C. (reported m.p. 59.3–59.9° C. (1) and 60.2° C. (9)). Calc. for $C_{17}H_{34}O_2$: C, 75.56; H, 12.59%. Found: C, 75.45; H, 12.72%. The *p*-bromophenacyl derivative had a m.p. 83.1–83.6° C. Calc. for $C_{25}H_{29}O_3Br$: C, 64.23; H, 8.41; Br, 17.1%. Found: C, 63.61; H, 8.64; Br, 17.4%.

Isopropylidene Ustilamide A

Methyl isopropylidene ustilate A (70 gm.), together with 1500 gm. of a 25% (wt.) solution of ammonia in methanol (prepared and kept below 0° C.), was heated to 180° C. in a sealed bomb for six and one-half hours. The product was poured into 3000 ml. of ice-cold water and the precipitated amide filtered off and washed with 1000 ml. of cold water. This material was dried and then boiled with 500 ml. of ether, and the slurry cooled to 5° C. when it was filtered. The precipitate was washed with 300 ml. of cold ether. Thirteen grams of unchanged methyl isopropylidene ustilate A were recovered from the ethereal filtrate and 55 gm. of crude amide were obtained, which crystallized from methanol as colorless plates, m.p. 99.7–100.3° C. Calc. for $C_{19}H_{37}O_3N$: C, 69.67; H, 11.39; N, 4.15%. Found: C, 69.62; H, 11.32; N, 4.17%.

Reaction of Isopropylidene Ustilamide A with Grignard Reagents

A solution of methylmagnesium bromide was prepared by slow addition of 236 gm. of a 17% solution of methyl bromide in dry ether (prepared by passing methyl bromide gas into dry ether at 0° C.) to 10.0 gm. of magnesium in 300 ml. ether. The Grignard reagent was allowed to settle, decanted, and its strength determined by titration.

A solution of methylmagnesium bromide in 440 ml. ether containing 47.5 gm.

(1.9 times theoretical) of the reagent was added to a solution of 33.9 gm. of isopropylidene ustilamide A, dissolved in 1500 ml. of a mixture of equal volumes of dry benzene and dry ether, with stirring, the solution being allowed to reflux during the addition. The solution was heated under reflux for a further eight hours, and the product was isolated in the usual manner. It was then dissolved in 50 ml. of ether and a small amount of unchanged amide was filtered off. The crude ketone (32.79 gm.) was dissolved in a small amount of benzene, transferred to an alumina column (14 cm. \times 5 cm.), and eluted with benzene. The material in the first 150 ml. of eluate (0.3 gm.) was discarded and the pure ketone (25.0 gm.) was isolated from the next 8000 ml. of eluate. The isopropylidene ether of 1,2-dihydroxy-16-ketoheptadecane had m.p. 40.0–40.5° C. Calc. for $C_{20}H_{38}O_3$: C, 74.12; H, 11.74%. Found: C, 73.9; H, 11.85%. Its semicarbazone had m.p. 123.5–124.0° C. Calc. for $C_{21}H_{41}O_3N_3$: C, 65.75; H, 10.77; N, 10.96%. Found: C, 65.79; H, 10.71; N, 11.00%. Three homologous ketones were prepared in a similar manner by using ethyl-, propyl-, and butyl-magnesium bromide Grignard reagents. These were purified by recrystallization and the melting points were respectively 37.0° C. (R = C_2H_5), 43.0° C. (R = C_3H_7), and 48.5° C. (R = C_4H_9).

1,2-Dihydroxy-16-ketoheptadecane

The 1,2-isopropylidene ether of 16-ketoheptadecane (8.0 gm.) was dissolved in 70 ml. of chloroform and the solution cooled to 5° C. Thirty milliliters of a 20% (wt.) solution of hydrochloric acid in 85% aqueous methanol was added and the solution allowed to stand at 20° C. for two hours. Water (100 ml.) was added and the product (m.p. 72–76° C.) extracted with chloroform. It was then dissolved in 50 ml. of 3% alcoholic potassium hydroxide solution and kept at 50° C. for 20 min. The solution was poured into 300 ml. of cold water and the methyl ketoglycol, 5.5 gm., m.p. 78–81° C., was filtered off and recrystallized three times from benzene, the pure product having m.p. 83.0–83.7° C. The products from the reaction of the ethyl, propyl, and butyl Grignards were treated in a similar manner to prepare the three other homologues whose constants are given in Table I.

15-Ketohexadecanoic Acid

Lead tetraacetate (300 mgm.) was dissolved in 25 ml. of dry benzene in a 50 ml. three-necked flask fitted with a stirrer, dropping funnel, and a condenser through which a glass tube passed and projected below the surface of the solution in the flask. 1,2-Dihydroxy-16-ketoheptadecane (500 mgm.) dissolved in 10 ml. of benzene (solution was maintained by the use of an infrared lamp) was added over a period of six hours from a dropping funnel. During addition the reaction mixture was stirred and maintained at a temperature of 50° C. and a stream of dried oxygen saturated with benzene was passed through the solution. At intervals of 45 min. 450 mgm. of lead tetraacetate was added to the solution. After the addition of ketoglycol was complete, the mixture was maintained at 50° C. with stirring for a further one and one-half hours, when 100 mgm. of ethylene glycol was added. After a further 10 min.

the warm solution was filtered and 10 ml. 30% acetic acid and then 100 ml. of water was added to the filtrate and the product extracted with benzene.

The benzene layer was washed once with water and the washings discarded. The keto acid was then extracted from the benzene layer by one washing with 50 ml. of 10% aqueous potassium hydroxide solution and two washes with water, disregarding emulsions formed owing to the rather low solubility of the potassium salt. The combined aqueous washings were acidified with sulphuric acid and extracted with benzene to yield 310 mgm. of the crude ketohexadecanoic acid. This was purified by conversion to its methyl ester, which was distilled and then reconverted to the free acid, which was crystallized four times from 95% methanol.

The ethyl, propyl, and butyl keto acids (Table I) were prepared similarly except that it was found unnecessary to convert to the methyl ester for the distillation of the crude product. The yield was found to decrease slightly as the molecular weight of the product increased.

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