[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

BRANCHED-CHAIN FATTY ACIDS. XV. SYNTHESES OF DIMETHYLOCTADECANOIC ACIDS. FURTHER STUDY OF THE CADMIUM REACTION AND OF THE HUANG-MINLON REDUCTION

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In order to permit further study of the effect of *alpha* and *beta* substituents on the rate of amide hydrolysis (1), 2,2-dimethyl- and 3,3-dimethyl-octadecanoic acid have been prepared, and a second synthesis of 2,3-dimethyloctadecanoic acid (2) has been investigated.

2,2-Dimethyloctadecanoic acid has previously been prepared by two groups of investigators. Buu-Hoï and Cagniant (3) prepared the amide by alkylation of isobutyrophenone with hexadecyl bromide, and cleavage of the resultant ketone with sodium amide. Hydrolysis yielded the acid, m.p. 50–51°. Birch and Robinson (4), who prepared the acid similarly except that stearophenone was dialkylated with methyl iodide, reported m.p. 42°. Later, Polgar, Robinson, and Seijo (5) prepared the acid by alkylation of methyl 2-methyloctadecanoate, and reported m.p. 48–49°. We have prepared this acid by dimethylation of octadecanenitrile, using lithium diethylamide according to Ziegler and Ohlinger (6). Hydrolysis of the disubstituted nitrile yielded acid of m.p. 51–55°. Although this value is higher than reported by the previous workers it was raised slowly by recrystallization, and no material of a constant m.p. was obtained in this way. Since introduction of the second methyl group is slow and difficult, it was suspected that the 2,2-dimethyloctadecanoic acid was contaminated with 2-methyloctadecanoic acid which would be essentially impossible to remove by crystallization or distillation. Since it has previously been shown (1) that 2,3-dimethyloctadecanamide is hydrolyzed much more slowly than the 2-methyl amide, and 3-methyloctadecanamide is hydrolyzed more slowly than the 2-methyl isomer, our crude 2,2-dimethyloctadecanamide was saponified and evolution of ammonia followed as previously described (1). When the rate of ammonia evolution indicated essentially complete hydrolysis of an amide initially hydrolyzing more rapidly, the saponification was interrupted and the mixture of amide and acid was separated by the use of Amberlite IRA-400 ion-exchange resin.[1] Recrystallization of the amide passing through the anion exchange resin yielded material of m.p. 85.5–86.0°, a value higher than previously reported (3, 4). Hydrolysis of the amide with potassium hydroxide in diethylene glycol yielded acid of m.p. 57.1–58.0°. It appears, then, that the 2,2-dimethyloctadecanoic acid prepared by Robinson and co-workers (4, 5) contained large

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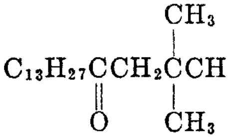
[1] Separation of fatty acids from neutral material has been traditionally difficult and tedious. Not only do the soaps cause stable emulsions but they also dissolve neutral material and the whole remains in the aqueous phase. Introduction of the strong anion exchange resins has rendered this separation very simple and rapid, and greatly facilitates the obtaining of pure samples of fatty acids. We are indebted to the Resinous Products Division, Rohm and Haas Company, for supplying us with samples of Amberlite IRA-400.

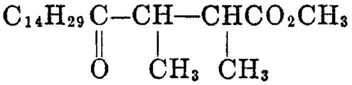
quantities of 2-methyloctadecanoic acid, but this could hardly have been the impurity which lowered the m.p. of the sample prepared by Buu-Hoï and Cagniant (3), for the latter workers alkylated isobutyrophenone with hexadecyl bromide. This is of interest, since the sample of 2,2-dimethyloctadecanoic acid prepared by the French workers was reported as producing typical tubercular lesions on injection in animals, whereas the sample prepared by the English workers did not (5). It is apparent that samples of fatty acids used for biological testing should be purified with great care, and it seems probable that deductions which have been based on such tests might well be subjected to further scrutiny.

3,3-Dimethyl- and 2,3-dimethyl-octadecanoic acid were prepared by reduction of keto esters, I and II, respectively. The keto esters were prepared from appropriate cadmium reagents (7) and ester acid chlorides. The ester acid chloride needed for the preparation of ester I is that of β,β-dimethylglutaric acid, and this acid was readily obtained by hypohalite oxidation of dimedone according to Walker and Wood (8). No complications were encountered in converting this dibasic acid to the anhydride, the half ester, and the ester acid chloride.



$$C_{13}H_{27}\underset{\underset{\displaystyle O}{\|}}{C}CH_2\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}CH_2CO_2CH_3$$

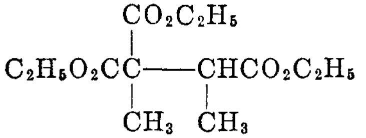
I



$$C_{14}H_{29}\underset{\underset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle CH_3}{|}}{CH}-\underset{\underset{\displaystyle CH_3}{|}}{CH}CO_2CH_3$$

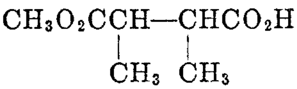
II

The ester acid chloride needed for the preparation of ester II is that of α,α′-dimethylsuccinic acid. Of the various methods which have been used for the preparation of this acid, probably the most promising is that of Bone and Sprankling (9), who alkylated ethyl cyanoacetate first with ethyl α-bromopropionate, then with methyl iodide to yield diethyl α-cyano-α,α′-dimethylsuccinate. Hydrolysis and decarboxylation yielded the desired acid. In the present work, a similar but somewhat shorter path was used, in that diethyl methylmalonate was alkylated with ethyl α-bromopropionate to yield the triester, III.



$$C_2H_5O_2C\overset{\overset{\displaystyle CO_2C_2H_5}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-\!\!-\underset{\underset{\displaystyle CH_3}{|}}{CH}CO_2C_2H_5$$

III



$$CH_3O_2C\underset{\underset{\displaystyle CH_3}{|}}{CH}-\underset{\underset{\displaystyle CH_3}{|}}{CH}CO_2H$$

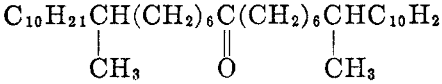
IV

When this alkylation was carried out in ethanol, using sodium ethoxide as the metalating agent, the yield was only 45% but when potassium *tert*-butoxide in *tert*-butyl alcohol was used as the metalating agent the yield was increased to 85%. The crude dimethylsuccinic acid, obtained by hydrolysis and decarboxylation of ester III, was converted to the anhydride and this was allowed to react with excess methanol to yield the half ester, IV, but this half ester appeared to revert to anhydride on standing or on heating for distillation. For synthesis of keto ester II, the crude, undistilled half ester IV was converted to the acid chloride below 40°, and this was used directly for reaction with di-*n*-tetradecylcadmium.

The present preparation of 2,3-dimethyloctadecanoic acid was undertaken in an effort to improve the very low yield obtained in the earlier preparation (2), but the present synthesis is only a slight improvement, for reduction of the keto ester II has not been accomplished in yields greater than 26%. Since ester I, exhibiting a similar amount of steric hindrance, was reduced in good yield by the Huang-Minlon procedure (10), the difficulty in reducing ester II appears to be associated with the γ-position of the keto group. Previously, it has been reported (11) that reduction of methyl 4-keto-8-methyloctadecanoate gave only 36% yield, and in the present work further study of this γ-keto ester has raised the yield to only 48%. Reduction of methyl 4-ketoöctadecanoate yields 75% of nearly pure stearic acid, and reduction of methyl 4-keto-8-methyltetradecanoate (12) has given a 68% yield. Thus, the best yields obtained by us for reduction of γ-keto esters are comparable with the lowest yields obtained for reduction of other types, and presence of steric hindrance in the γ-keto esters leads to much lower yields. A very highly hindered δ-keto ester has been reduced by this method in 41.5% yield (13).

The low yields obtained in the reduction of γ-keto esters are accompanied by considerable residues from distillation of the reduced esters. When the heating period for reduction of ester II was extended, in an effort to improve the yield, the yield was lowered and the distillation residue was larger. The distillation residues from several preparations were investigated in hopes of discovering the cause of the low and variable yields received in these reductions, and some findings of general interest may be reported.

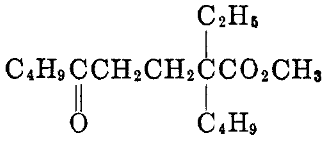
When the stearic acid obtained by reduction of methyl 4-ketoöctadecanoate was separated from neutral material by use of Amberlite IRA-400, the crude acid eluted from the column melted at 66–68.5°, and one crystallization gave an 85% recovery of pure stearic acid, m.p. 68.9–69.5°. Thus, the by-products are nearly entirely neutral material. From the distillation residues after reduction of methyl 4-keto-8-methyloctadecanoate there was isolated a hydrocarbon, $C_{37}H_{76}$, presumably 11,25-dimethylpentatriacontane resulting from reduction of the ketone V. The ketone would be formed during heating of the initial product,



$$C_{10}H_{21}\underset{\substack{|\\ CH_3}}{C}H(CH_2)_6\underset{\substack{\|\\ O}}{C}(CH_2)_6\underset{\substack{|\\ CH_3}}{C}HC_{10}H_{21}$$

V

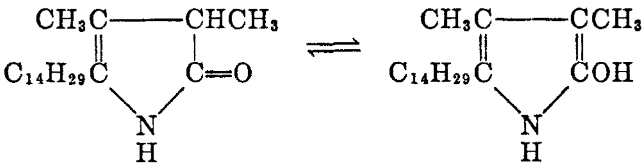
8-methyloctadecanoic acid, with alkali, as is done in this type of reduction. One of us (13) has previously recommended for aliphatic keto acids a longer heating period and higher temperature than originally used by Huang-Minlon (10). This suggestion resulted from the fact that keto ester VI was reduced in 90% yield under the more drastic conditions. It is now apparent that the high yield in this instance is dependent on the fact that the keto in ester VI is unhindered but the acid group is highly hindered, the most favorable possible combination of circumstances for this type of reduction. The conditions originally proposed by Huang-Minlon are adequate in the aliphatic series for reduction of all but highly hindered keto groups, and more drastic conditions result in lower yield or less pure product.



$$\mathrm{C_4H_9\underset{\underset{\displaystyle O}{\|}}{C}CH_2CH_2\overset{\overset{\displaystyle C_2H_5}{|}}{\underset{\underset{\displaystyle C_4H_9}{|}}{C}}CO_2CH_3}$$

VI

Since it is known (14) that γ-keto acids give a cyclic hydrazide with hydrazine, it was suspected that the difficulty in reducing the γ-keto acids might be associated with an abnormal reaction of this intermediate, although the cyclic hydrazide from levulinic acid decomposes normally on heating with sodium ethoxide, to give valeric acid (14). Steric hindrance might prevent normal hydrolysis of the hydrazide, and permit side reactions to become more significant. From distillation residues after reduction of keto ester II, there was isolated a solid compound containing nitrogen and giving an analysis in agreement with the formula, $C_{20}H_{37}NO$. The unsaturated lactam or pyrollone shown in formula VII has such a composition, and the possibility of this structure is supported



VII

by the report (15) that hydrazones may be reduced to amines under certain conditions. Carrière (16) has prepared pyrrolones by saponification of unsaturated γ-amino esters with concentrated potassium hydroxide, and Almström (17) has prepared pyrrolones directly from γ-keto acids and aniline. Compound VII was saponified little, if any, by heating for 46 hours with alcoholic potassium hydroxide, but the structure indicated would be expected to be highly hindered.

In some runs during the preparation of keto esters I and II, very low yields (5–15%) were obtained in the cadmium reaction. It has been established that the low yields were caused by thermal cracking of the dialkylcadmium reagent by heating on a steam-bath. This difficulty is less pronounced with lower molecular weight alkyls, but in all cases the residue, obtained after ether is distilled from the cadmium reagent, should not be heated; instead benzene should be added and the reaction with the acid chloride completed at once. It seems highly probable that the erratic yields obtained from cadmium reactions in various laboratories have been caused by too much heating of the cadmium reagent after distillation of ether. Prolonged boiling in ether appears to cause little, if any, cracking of cadmium reagents from primary alkyls. The principal product of reactions in which the cadmium reagent has been overheated is a hydrocarbon corresponding to the alkyl radical, and this has been shown by hydrogenation to be an approximately equimolar mixture of alkane and alkene. This would result from disproportionation of the radicals initially formed by cracking of the organometallic reagent.

EXPERIMENTAL

All melting points are corrected, and all boiling points are uncorrected. Analyses were performed by the Microanalytical Division of the Department of Chemistry and Chemical Engineering of the University of California. Unless otherwise specified, all distillations were through a 65-cm. Podbielniak type column which had a simple tantalum wire spiral and a partial reflux head.

2,2-Dimethyloctadecanoic acid. Of various modifications of this preparation which were investigated, the following appears best. To 485 ml. of 0.652 molar phenyllithium (0.315 mole), prepared as described by Rapoport and Williams (18), in an atmosphere of nitrogen, there was added during 40 minutes, with stirring and cooling in ice, 32 ml. (0.32 mole) of diethylamine in 50 ml. of ether. Immediately after addition was complete, the Gilman test (19) was negative. Approximately half of this solution of lithium diethylamide was removed and stored under nitrogen. To the remaining half there was added without cooling a solution of 31.9 g. (0.12 mole) of octadecanenitrile (fractionated, b.p. 180–182° at 2 mm.) in 50 ml. of ether, during 30 minutes. After the first five minutes a white precipitate began to separate and the Gilman test had become positive. After addition was complete, stirring was continued at room temperature for one hour.

To the solution of the lithium derivative of octadecanenitrile, cooled in an ice-bath, there was added dropwise with stirring a cold solution of 19 g. (0.20 mole) of methyl bromide in 25 ml. of ether. The Gilman test was negative as soon as addition was complete.

To the reaction mixture there was next added dropwise the other half of the lithium diethylamide. After stirring at room temperature for two hours, addition of a second 19 g. of methyl bromide was made, with cooling. After stirring had been continued for 30 minutes at room temperature and 45 minutes under reflux, the reaction mixture was washed with water, 2 *N* hydrochloric acid, and saturated aqueous sodium chloride solution. Ether was removed by distillation, the last traces at reduced pressure.

The crude nitrile was dissolved in 375 ml. of concentrated sulfuric acid, and the solution was stirred for 20 minutes in an oil-bath at 100°. The cooled solution was poured into 2.5 liters of ice and water, and the precipitated amide, obtained in nearly quantitative yield, was filtered, washed, and dried. The crude amide was heated in a steel flask in 600 ml. of 95% ethanol containing 33 g. of potassium hydroxide, the flask being fitted with a reflux-distillation head of the type described by Cason and Wolfhagen (1). Ammonia evolution was followed as described by these authors. At the end of 80-hours heating under reflux, 44% of the theoretical amount of ammonia had been titrated, and the rate of ammonia evolution had dropped to less than one half the initial value of about 1% per hour. At this point, most of the alcohol was distilled, the reaction mixture was diluted with water and acidified, and the mixture of amide and acid was extracted with ether. The wet ether solution was passed through a column of 225 g. (wet weight) of Amberlite IRA-400 which had previously been washed with alkali and then with water until the eluate was neutral. The eluate was passed through the column a second time, then the column was washed with two 100-ml. portions of ether, the second portion leaving only 0.2 g. of residue on evaporation. Removal of ether from the total eluate left a residue of 21.1 g. of amide, m.p. 80–84°. After two crystallizations from methanol and two from hexane there was obtained 14.8 g. (30% yield from octadecanenitrile) of *pure 2,2-dimethyloctadecanamide*, m.p. 85.5–86.0° [literature, m.p. 81° (4), 85° (3)].

Elution of the ion-exchange column with a mixture of ether, methanol, and aqueous hydrochloric acid yielded 15.3 g. of mixed acid which was not further investigated.

A 5-g. sample of the amide was hydrolyzed by heating for four hours at a bath temperature of 210–220° with a mixture of 30 ml. of diethylene glycol and 3.6 g. of potassium hydroxide. The theoretical amount of ammonia was titrated. Dilution with water and acidification of the cooled reaction mixture gave a quantitative yield of crude acid which was esterified by heating under reflux for six hours with 25 equivalents of methanol containing 10% by weight of concentrated sulfuric acid. Distillation gave 4.7 g. (88% from amide) of *methyl 2,2-dimethyloctadecanoate*, b.p. 172–172.5° (3 mm.) For analysis, there was used a center cut, n_D^{21} 1.4438.

Anal. Calc'd for $C_{21}H_{42}O_2$: C, 77.24; H, 12.97.
Found: C, 77.22; H, 12.93.

By hydrolysis of the ester and three crystallizations from acetone, there was obtained *2,2-dimethyloctadecanoic acid*, m.p. 57.1–58.0°.

Anal. Calc'd for $C_{20}H_{40}O_2$: Equiv. wt., 312.5. Found: Equiv. wt., 314.0.

The *p-bromoanilide* was prepared as has been described (13). After crystallization from benzene, there was obtained a 67% yield of fine needles, m.p. 84.9–85.4°.

Anal. Calc'd for $C_{26}H_{44}BrNO$: N, 3.00. Found: N, 2.90.

2,2-Dimethyloctadecanenitrile was isolated from a dimethylation of octadecanenitrile carried out similarly to that described above. The crude nitrile obtained from the reaction was distilled, b.p. 175–180° (1.6 mm.), and the distillate was crystallized repeatedly from methanol until there was isolated a small yield of colorless blades of constant m.p. 37.0–38.6°.

Anal. Calc'd for $C_{20}H_{39}N$: N, 4.77. Found: N, 4.68.

The quantity of nitrile thus isolated was too small to make this method of purification practical, but the purity of the final product was established by conversion of a sample to the amide by use of concentrated sulfuric acid, as described above. After crystallization from hexane, the amide so obtained melted at 85.5–86.0°, in agreement with the best sample obtained by the purification method described above.

Methyl hydrogen β,β-dimethylglutarate. β,β-Dimethylglutaric anhydride was prepared by heating 72 g. (0.45 mole) of β,β-dimethylglutaric acid[2] (8) with three mole-equivalents of acetyl chloride on a steam-bath for 90 minutes. The reaction mixture was treated with about 30 ml. of petroleum ether (b.p. 30–70°) and allowed to crystallize. After cooling in an ice-bath, there was collected 51.1 g. of anhydride, m.p. 126.0–126.5°, not raised by further crystallization [literature (20), m.p. 124°]. By evaporation of the mother liquor and recrystallization of the residue from anhydrous ether, there was obtained an additional 10.7 g. of anhydride in three crops, the least pure melting at 123–125°; total yield, 61.8 g. (97%).

The half ester was best prepared by heating under reflux for five hours a mixture of 21.6 g. (0.152 mole) of the anhydride and 18.5 ml. (0.45 mole) of methanol. Distillation yielded 5 g. of diester (distilling principally at 81° at 6 mm.) and 21.2 g. (80%) of half ester, b.p. 126–127° (4.5 mm.).

Anal. Calc'd for $C_8H_{14}O_4$: Equiv. wt., 174.2. Found: Equiv. wt., 172.8.

When an attempt was made to prepare this half ester as has been described for methyl hydrogen succinate (21), much anhydride remained unreacted on account of steric hindrance. It is best to use excess methanol and an adequate heating time in order to insure reaction of all anhydride, for diester is readily separable from half ester by distillation whereas anhydride is not.

γ-Carbomethoxy-β,β-dimethylbutyryl chloride was prepared by allowing 56.8 g. (0.326 mole) of the above-described half ester to stand overnight with 77.6 g. (0.65 mole) of thionyl

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[2] We are indebted to Mr. Charles N. Whiteside for preparation of this acid.

chloride. On distillation there was obtained 57.8 g. (92%) of ester acid chloride, b.p. 75–76° (3 mm.).

Anal. Calc'd for $C_8H_{13}ClO_3$: Equiv. wt., 96.3. Found: Equiv. wt., 96.2.

Methyl 3,3-dimethyl-5-ketoöctadecanoate (I). A Grignard reagent was prepared in an atmosphere of nitrogen in the usual manner from 4.9 g. (0.2 mole) of magnesium turnings and 52.7 g. (0.2 mole) of *n*-tridecyl bromide (22), and this was converted to the cadmium reagent with 29.2 g. (0.16 mole) of anhydrous cadmium chloride. Ether was distilled until distillation on a steam-bath became slow, then 65 ml. of benzene was added immediately, and an additional 10 ml. of distillate was collected. This mixture was cooled to about 20°, and then there was added in one portion to the stirred mixture a solution of 19.3 g. (0.1 mole) of γ-carbomethoxy-β,β-dimethylbutyryl chloride in 70 ml. of benzene. The temperature of the mixture rose rapidly to 40° and was maintained at 38–40° for about 80 minutes, cooling being necessary during the first 20 minutes. The temperature was then raised to 65° during one hour, after which time the mixture was worked up as usual (7). On distillation, there was obtained 14.5 g. of fore-run consisting mostly of *tridecane*, b.p. 115° (15.5 mm.), and 30.1 g. (88%) of *keto ester* I, b.p. 191–193° (2.5 mm.), n_D^{25} 1.4490.

Anal. Calc'd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84.
Found: C, 74.06; H, 11.85.

In a run similar to that described above, the cadmium reagent remaining after distillation of ether was heated on a steam-bath for about 75 minutes in order to remove as much ether as possible. When the reaction products were distilled, there was less than 10% of keto ester and 28.8 g. of material distilling largely at about 111° (13 mm.). This was shown to be a mixture of *tridecane* and *tridecene* in the following manner.

The material was redistilled and a center cut taken, b.p. 116.5–117° (17.5 mm.), n_D^{22} 1.4292. On hydrogenation of a 5-g. sample of this material with commerical platinum oxide catalyst, there was absorbed 347 ml. of hydrogen (corrected to 0° and for hydrogen absorbed by catalyst). This corresponds to 56% of alkene in the sample. The hydrocarbon recovered after hydrogenation had b.p. 120–121° (21 mm.), n_D^{22} 1.4256. From the literature (23, 24), for tridecane, b.p. 114° (15 mm.), 130° (30 mm.), n_D^{20} 1.4266; for tridecene, n_D^{20} 1.4340. Thus, the calculation of tridecene in the original sample, from index of refraction, gives 54%, in good agreement with the value obtained by hydrogenation.

3,3-Dimethyl-5-ketoöctadecanoic acid, obtained by saponification of its ester, after two crystallizations from hexane and one from acetone, melted at 48.5–48.9°.

Anal. Calc'd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73; Equiv. wt., 326.5.
Found: C, 73.75; H, 11.64; Equiv. wt., 325.7.

Methyl 3,3-dimethyloctadecanoate. A 47.3-g. sample of keto ester I was reduced as described by Huang-Minlon (10) except that the final heating period was for seven hours at 218–221°. The crude acid, obtained by dilution with water and acidification of the cooled reaction mixture, was esterified by heating with 25 equivalents of methanol containing 10% by weight of sulfuric acid. Distillation yielded 35.6 g. (78.5% from keto ester) of reduced ester, b.p. 176.5–180° (2.5 mm.). For analysis, there was used a center cut, b.p. 178° (2.5 mm.), n_D^{21} 1.4475.

Anal. Calc'd for $C_{21}H_{42}O_2$: C, 77.24; H, 12.97.
Found: C, 77.81; H, 12.91.

3,3-Dimethyloctadecanoic acid was obtained by saponification of 32.8 g. of the ester. After one crystallization from acetone, there was obtained 28.1 g. (89.5%) of m.p. 41.9–43.8°, and after two further crystallizations there was obtained 24.7 g. with constant m.p. 44.0–44.8°.

Anal. Calc'd for $C_{20}H_{40}O_2$: Equiv. wt., 312.5. Found: Equiv. wt., 313.3.

The *amide*, prepared essentially as described previously (2), after four crystallizations from methanol, had the constant m.p. 57.8–58.5°.

Anal. Calc'd for $C_{20}H_{41}NO$: N, 4.50. Found: N, 4.41.

The *p-bromoanilide*, prepared by the usual procedure (13), was crystallized three times from methanol to give platelets with the constant m.p. 89.4–89.7°.

Anal. Calc'd for $C_{26}H_{44}BrNO$: N, 3.00. Found: N, 3.07.

Diethyl α-carbethoxy-α,α'-dimethylsuccinate (III). In 1200 ml. of *tert*-butyl alcohol (distilled from sodium) was dissolved 35.8 g. (0.92 mole) of potassium, and to the cooled solution there was rapidly added 163.8 g. (0.94 mole) of diethyl methylmalonate (prepared from ethyl oxalpropionate). To this mixture there was added with stirring, during about five minutes, 140.8 g. (0.78 mole) of ethyl α-bromopropionate, and the mixture was heated under reflux for two hours. After most of the alcohol had been distilled from the mixture, with stirring, the residue was shaken out with water and benzene. From the benzene extract there was obtained 181.2 g. (85%) of *triester* III, b.p. 151–152° (12 mm.) [literature (25), b.p. 190° (50–60 mm.), 279° (760 mm.)]. In a 5-mole run, the yield was 80%.

α,α'-Dimethylsuccinic anhydride. Triester III (162 g.) was hydrolyzed by heating under reflux, with stirring, with a mixture of 450 ml. of water and 450 ml. of concentrated hydrochloric acid until the mixture had become homogeneous (usually 4–6 hours). The reaction mixture was then distilled to dryness, and the residue was decarboxylated by heating at 180–200° for about one hour. The crude acid was heated on the steam-bath for one hour with 120 ml. of acetic anhydride. Distillation of the mixture gave 52.1 g. (68.5%) of anhydride, b.p. 95–98° (5 mm.), which set to a semi-solid on standing. No effort was made to separate this mixture of stereoisomers (26).

Methyl 4-keto-2,3-dimethyloctadecanoate (II). This preparation was carried out essentially as described for preparation of the isomeric ester, I, starting with 55.4 g. (0.2 mole) of *n*-tetradecyl bromide. For preparation of the required ester acid chloride, 12.8 g. (0.1 mole) of α,α'-dimethylsuccinic anhydride was heated under reflux for two hours with 5 ml. of methanol, excess methanol was removed in a vacuum, and the residual crude half ester was allowed to stand overnight with 25 ml. of thionyl chloride. Excess thionyl chloride was removed at reduced pressure, and from the residue were distilled at reduced pressure two 25-ml. portions of benzene. The residual acid chloride was used for the cadmium reaction. The yield of *keto ester* II was 22.0 g. (64.5%), b.p. 196–197° (3 mm.).

Anal. Calc'd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84.
Found: C, 73.67; H, 11.53.

2,3-Dimethyloctadecanoic acid. A 15.7-g. sample of keto ester II was reduced by the modified Huang-Minlon procedure previously described (13), and the crude reaction product was esterified by heating for five hours with 40 ml. of methanol and 3 ml. of concentrated sulfuric acid. Distillation yielded 3.9 g. (26%) of discolored methyl 2,3-dimethyloctadecanoate, b.p. 181–184° (3 mm.). In another run, which was carried out in an atmosphere of nitrogen, the heating period at 210–220° was extended to 30 hours, and the yield was only 12%.

A total of 5.9 g. of ester was saponified with alcoholic potassium hydroxide. After the acid had been crystallized three times from acetone, there was obtained 0.37 g. of one racemic form, m.p. 64.5–64.7°. The best sample previously obtained (2) melted at 63.0–64.0°, and a mixture of the two samples melted at 63.3–64.2°.

Investigation of the Huang-Minlon reduction. A. *Reduction of methyl 4-ketoöctadecanoate* (5.0 g.) was carried out as described by Huang-Minlon (10), using potassium hydroxide and diethylene glycol. The final heating period was for 5 hours at 195–200°. After the cooled reaction mixture had been diluted with water and acidified it was extracted with ether, and the wet ether extract was passed through a column of the basic form of Amberlite IRA-400. The column was washed with 400 ml. of ether, then the acid was eluted with a mixture of 200 ml. of ether, 80 ml. of 95% alcohol, and 40 ml. of concentrated hydrochloric acid. The column was washed with an additional 150 ml. of ether. After removal of hydrochloric acid from the eluate by washing with water, the solvent was evaporated to dryness to yield 3.4 g. (75%) of stearic acid, m.p. 66–68.5°. One crystallization from acetone gave 2.85 g. of acid, m.p. 68.9–69.5°.

The material originally passing through the ion-exchange column weighed 0.58 g. and was shown by titration to be neutral.

When a similar run was made, except that the heating period was 7 hours at 215–220°, the same yield of crude acid was obtained, but the m.p. was 59–67°, and two crystallizations were required to yield pure stearic acid.

B. About 20 g. of *residues* from distillation of the ester from several reductions of *methyl 4-keto-8-methyloctadecanoate* were distilled in a von Braun flask to yield 6.4 g. of greenish-yellow material, b.p. 160–230° (1 mm.), which began to crystallize after standing several days. After repeated crystallization from ethanol, hexane, and acetone, there were obtained clusters of small needles with the constant m.p. 41.5–41.7°. The analysis is in agreement with that for *11,25-dimethylpentatriacontane.*

Anal. Calc'd for $C_{37}H_{76}$: C, 85.29; H, 14.71.
Found: C, 85.41; H, 14.70.

C. From *reduction* of 7.2 g. of *ester II* and esterification of the product, there was obtained 1.5 g. of semi-solid, b.p. 200–220° (0.5 mm.). After repeated crystallization from acetone and hexane there was obtained 0.1 g. of colorless needles with the constant m.p. 70.8–72.2°. The analysis is in agreement with the structure indicated in *formula VII.*

Anal. Calc'd for $C_{20}H_{37}NO$: C, 78.11; H, 12.12; N, 4.55.
Found: C, 78.32; H, 12.37; N, 4.58.

A 0.1-g. sample of this substance of m.p. 64–68° was refluxed for 46 hours in 10% alcoholic potassium hydroxide. On dilution of the alkaline solution there separated a solid of m.p. 62–67°, and acidification of the alkaline filtrate gave only a barely perceptible trace of oil which did not solidify.

SUMMARY

Syntheses have been developed for 2,3-dimethyl-, 2,2-dimethyl-, and 3,3-dimethyl-octadecanoic acid. Of these acids, the last-mentioned has not been previously prepared, and the second has not been previously prepared in a pure state.

A further study has been made of side reactions occurring in the cadmium reaction for preparation of ketones and in the Huang-Minlon modification of the Wolff-Kishner reduction.

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