[Contribution from Avery Laboratory, University of Nebraska]

SYNTHESIS OF *dl*-3,3,4-TRIMETHYLCYCLOPENTANONE

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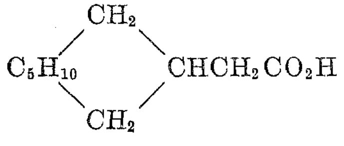
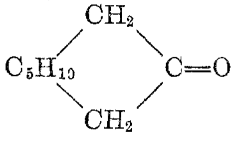
From the degradation of a naphthenic acid (I), isolated from a wide variety of petroleum sources, von Braun and coworkers (1) obtained a ketone (II) to which they assigned the structure of the then unknown 3,3,4-trimethylcyclopentanone (III) (on the basis of the non-identity of II with any of the other possibilities and other supporting evidence (2, 3)). von Braun's attempts to synthesize III were unsuccessful (3). Later Buchman and Sargent (4, 5) reported the synthesis of III by three different routes and showed that II and III could not be identical.[1] More recently, however, Mukherji (6) reported, in a brief note,[2] a fourth synthesis of III by which she obtained a ketone whose properties were in substantial agreement with those reported by von Braun (1) for II.


I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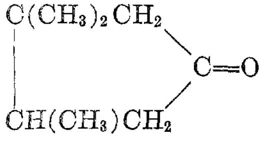
III

In connection with a study of the $C_9H_{17}CO_2H$ fraction from Aruba petroleum [which is thought to contain I (7)], we have synthesized III by a fifth route, which is outlined in the flow sheet. The starting material used in this synthesis, as well as in that of Mukherji (6), was ethyl β,β-dimethyllevulinate (X) (6, 8, 9). In the course of the preparation of relatively large quantities of X, we have found the following procedure to be the most satisfactory.

α,α-Dimethylsuccinic acid (V) was prepared in 53–69% yield by the excellent procedure of Smith and Horwitz (10) from acetone, ethyl cyanoacetate (IV), and potassium cyanide. Normally, however, V was not isolated as such, the crude acid being converted by heating with excess acetic anhydride (11) into α,α-dimethylsuccinic anhydride (VI) in 92–97% yield (53–61% over-all from IV). Heating VI under reflux with ethanol (12) yielded a mixture of the two monoethyl esters (VII and VIII) of V, a procedure found to be superior to others used previously (8, 11, 13). The two isomers (VII and VIII) were readily separated by virtue of the greater solubility of VII in petroleum ether (11, 12). The yield of VIII was 72–77%. The undesired isomer, VII, (and traces of the

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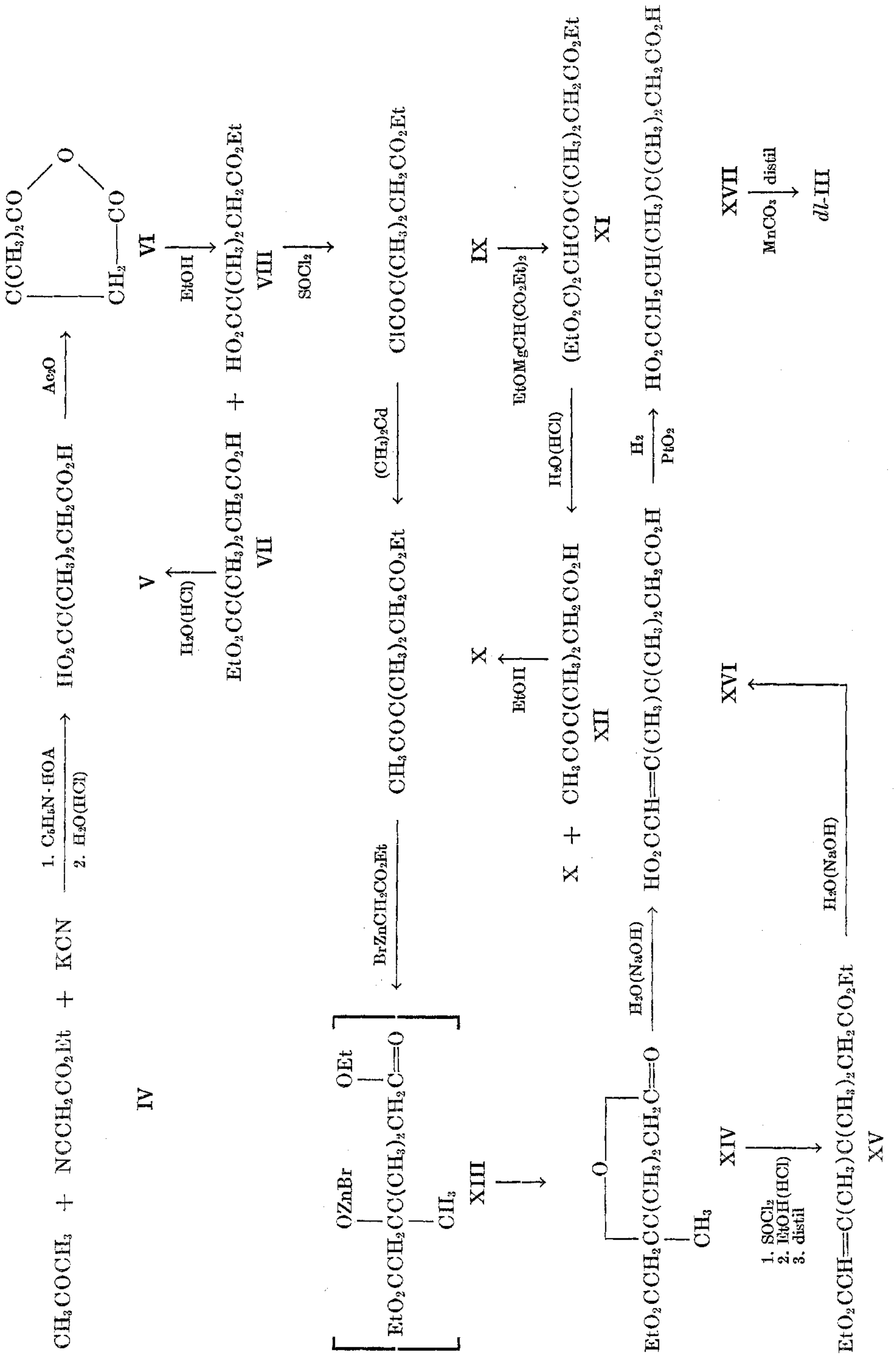
[1] Ruzicka and coworkers (28, 29) have reported the preparation of 3,3,4-trimethylcyclopentanone (III) from an optically active acid (*d*-XVII) obtained in the course of degradative studies of irone (28) and tetrahydroirone (29). The reasonably close agreement of the properties of their ketone (presumably optically active) with those reported by Buchman and Sargent (4, 5) for *dl*-III may be taken as mutual confirmation of the structural assignments made by both groups of workers.

[2] Quantities of reactants, reaction conditions, reaction times, analyses, and physica constants other than boiling and melting points are not reported by Mukherji.


CH3COCH3 + NCCH2CO2Et + KCN
IV
1. C5H5N·HOA
2. H2O(HCl)
HO2CC(CH3)2CH2CO2H
V
Ac2O
C(CH3)2CO
O
CH2——CO
VI
EtOH
H2O(HCl)
EtO2CC(CH3)2CH2CO2H + HO2CC(CH3)2CH2CO2Et
VII
VIII
SOCl2
ClCOC(CH3)2CH2CO2Et
IX
(CH3)2Cd
CH3COC(CH3)2CH2CO2Et
X
EtOH
EtOMgCH(CO2Et)2
(EtO2C)2CHCOC(CH3)2CH2CO2Et
XI
H2O(HCl)
X + CH3COC(CH3)2CH2CO2H
XII
BrZnCH2CO2Et
OZnBr
OEt
EtO2CCH2CC(CH3)2CH2C=O
CH3
XIII
O
EtO2CCH2CC(CH3)2CH2C=O
CH3
XIV
H2O(NaOH)
HO2CCH=C(CH3)C(CH3)2CH2CO2H
H2
PtO2
HO2CCH2CH(CH3)C(CH3)2CH2CO2H
XVI
XVII
MnCO3
distil
dl-III
1. SOCl2
2. EtOH(HCl)
3. distil
EtO2CCH=C(CH3)C(CH3)2CH2CO2Et
XV
H2O(NaOH)

diethyl ester) was hydrolyzed to V with concentrated hydrochloric acid and the recovered V was put through the cycle again. In this fashion the yield of VIII was increased to 86–90%.

The procedures reported previously for the transformation of VIII into X involved the reaction of the crude acid chloride (IX), prepared with phosphorus trichloride (8) or thionyl chloride (11), with dimethylzinc (8), a methylzinc halide (9), or ethyl ethoxymagnesium malonate (6). In this work IX was prepared from the reaction of VIII with excess thionyl chloride at temperatures below 40°, following the procedure used by Cason, Sumrell, and Mitchell (14) with the monoethyl ester of α,β-dimethylsuccinic acid. Crude IX reacted readily with dimethylcadmium (15) to form X in 47–62% yield. As an alternate route, the procedure outlined by Mukherji (6) was found to be very satisfactory. Crude IX reacted with ethyl ethoxymagnesium malonate (16, 17) to form the unisolated intermediate XI, and the latter was hydrolyzed and decarboxylated with a mixture of acetic and sulfuric acids (16) or preferably with concentrated hydrochloric acid (18). Distillation of the product gave a 58% yield of XII and a 23% yield of X. The presence of the latter in the product from the hydrolysis and decarboxylation must indicate that the two carbethoxy groups in the malonic ester portion of the molecule (XI) are more readily hydrolyzed than the carbethoxy group at the other end of the molecule. Satisfactory conditions for the selective hydrolysis and decarboxylation of XI to X in high yield were not found, and, in general, it was more satisfactory to esterify the crude mixture of X and XII with ethanol (and hydrogen chloride). In this fashion the over-all yield of X from VIII was 67–75%; the yield in the esterification step alone was 90%.

Although, from the standpoint of the time involved and the number of manipulations required, the dimethylcadmium reaction appears to be superior, the reaction was much more susceptible to reaction variables (solvent, temperature, stirring, etc.) than the malonic ester method and in a long series of experiments gave consistently lower yields, particularly in large runs where adequate stirring was difficult. Lower yields (47–51%) were obtained when methylmagnesium iodide was used in the preparation of the dimethylcadmium than when methylmagnesium bromide was used (57–62%).

The principal step in the synthesis of III from X as reported by Mukherji (6) consisted of the condensation of X with ethyl cyanoacetate, as a basis for which she cited the work of Cope, Hofmann, Wyckoff, and Hardenbergh (19). However, in the reference cited, Cope and coworkers reported that the structurally analogous pinacolone did not condense with ethyl cyanoacetate under the conditions of their experiments. By use of a reaction time of 80.5 hours and incremental addition of catalyst, Cragoe, Robb, and Sprague (20) have obtained a 13% yield of the pinacolone condensation product. On the other hand, Newman and Rosher (21) have shown that pinacolone undergoes the Reformatsky reaction with methyl and ethyl bromoacetate, giving yields as high as 63%. These results have been confirmed in this Laboratory. On the basis of the more favorable appearance of the results from the Reformatsky reaction, that reaction was chosen for the synthesis of III from X in preference to the route used by Mukherji.

The γ-keto ester X reacted with ethyl bromoacetate and zinc to form the lactone XIV in 50–54% yield.[3] The unreacted X recovered from the Reformatsky reaction (30–38% of the original amount) was treated with additional ethyl bromoacetate and zinc to give a total yield of XIV of 62–69%. Approximately equimolar quantities of reactants appeared to give the best results. Large excesses of zinc and/or ethyl bromoacetate did not give higher yields but complicated isolation of the product and lowered the recovery of unreacted X. Excess X had little effect. We were unable to determine with certainty whether or not the product contained small amounts of the unsaturated ester XV or of the corresponding hydroxy ester, although the boiling range of the crude product indicated that they might be present.

The lactone XIV was converted into the unsaturated ester XV (or an unsaturated ester of identical carbon skeleton) by the procedure of Cason, Adams, Bennett, and Register (22), which involved scission of the lactone ring with excess thionyl chloride, conversion of the resultant intermediate into the γ-chloro (or β-chloro) ester with ethanol saturated with hydrogen chloride at 0°, and thermal dehydrohalogenation of the chloro ester. The yield of XV was 74–88%. A large excess of thionyl chloride was found desirable in the first stage of the reaction to insure a high yield of XV.

The hydrolysis of XV proceeded slowly in hot 25% aqueous sodium hydroxide, but quite rapidly in aqueous-alcoholic sodium hydroxide, to give, upon acidification, the solid unsaturated acid XVI (or an unsaturated acid of identical carbon skeleton) in 90% yield.

A more direct route to XVI from XIV was found to consist of the hydrolysis of XIV with 25% aqueous or aqueous-alcoholic sodium hydroxide. In contrast with the hydrolysis of XV, the hydrolysis of XIV with aqueous alkali when once started proceeded almost explosively. Acidification of the reaction mixture yielded a mixture of approximately equal amounts of two acids, one a liquid and the other a solid. The latter was found to be XVI and was obtained in 55–60% yield. The nature of the liquid acid was not determined, but, on the assumption that it might be the lactonic acid corresponding to XIV, it was treated with thionyl chloride followed by ethanolic hydrogen chloride and the resultant product was thermally dehydrohalogenated. A 61% yield of XV was obtained (yield based on same assumption). An alternate possibility is that the liquid and solid acids were *cis-trans* isomers (21); however, the liquid acid was not hydrogenated in the presence of platinum oxide catalyst (even after prolonged treatment with Raney nickel and hydrogen to remove any catalyst poisons).

The formation of the unsaturated acid (XVI) during the hydrolysis of the

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[3] The reaction of γ-keto and δ-keto esters with α-bromoesters and zinc to yield γ- and δ-lactones, respectively, is apparently an old and well-tried procedure. [For a leading reference to the reaction of ethyl levulinate and its analogs see (23)]. It is unfortunate, therefore, that the excellent discussion of the Reformatsky reaction in *Organic Reactions* (24) does not include an example of lactone formation of this type.

lactone (XIV) may be explained as the dehydration of a β-hydroxy acid salt, since the acid formed on hydrolysis of the γ-lactone is both a γ- and a β-hydroxy acid. Dehydration of β-hydroxy esters and acids with aqueous alkali has been reported previously by Shroeter (25).

The hydrogenation of XV in the presence of platinum oxide proceeded rapidly to form β,β,γ-trimethyladipic acid (XVII), a white, crystalline solid, melting at 126.5–127.5°, in 86–95% yield. Buchman and Sargent (4) reported the melting point of XVII to be 126.5–127°; Mukherji (6) reported the melting point to be 103°.

Cyclization of XVII by distillation with a small amount of manganous carbonate (4) at 280–300° gave *dl*-III in 95% yield. A number of derivatives of III were prepared; the physical constants of these are listed in Table I together with those reported by Buchman and Sargent (4) and by Mukherji (6) for their synthetic ketones and by von Braun (1) for II. From the table it is apparent that our results afford additional confirmation of the earlier observations of Buchman and Sargent and further substantiate their statement that *dl*-III and II cannot be identical and that I was incorrectly identified by von Braun.

TABLE I

PROPERTIES OF *dl*-3,3,4-TRIMETHYLCYCLOPENTANONE AND DERIVATIVES

KETONE	B.P., °C.	SEMICARBAZONE, M.P., °C.	OXIME, M.P., °C.	BIS-*p*-NITROBENZAL DERIV., M.P., °C.
Ketone from naphthenic acids	172–174	162–163	116–120[a]	188–190
3,3,4-Trimethylcyclopentanone (Mukherji)	174	172	—	190–191
3,3,4-Trimethylcyclopentanone (Buchman and Sargent)	172–173	213.5–214.0	99.8–100.0	α-form, 204.7–205.1 β-form, 202.0–202.5
3,3,4-Trimethylcyclopentanone (Baumgarten and Gleason)	172–173	213.0–213.5	99.5–100.0	α-form, 205.0–205.5 β-form, 202.8–203.2

[a] B.p./14mm.

Although we are not prepared at this time to speculate on the true structure of II (and I), it does appear to us that the reexamination of the other ten possible ketones and their stereoisomers is in order. In this connection it should be noted that the synthesis utilized here for III appears to be adaptable to the synthesis of six of the ten ketones.[4]

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[4] After this paper had been submitted for publication, the abstract of a paper by Okazaki (26) (originally published in Japan in 1943) appeared. Okazaki reported the preparation of 3-ethyl-4-methylcyclopentanone, one of the eleven possibilities for the von Braun ketone, by a route similar to that described here for *dl*-III. Okazaki, however, cyclized the equivalent of XVI and then hydrogenated the unsaturated ketone. On the basis of experimental work to be reported later, we believe that better results are obtained when the sequence utilized in the present work is followed; i.e., reduction before cyclization.

EXPERIMENTAL

Melting points are corrected; boiling points are uncorrected. Analyses marked with an asterisk (*) were by the Clark Microanalytical Laboratory, Urbana, Illinois; the others were made by the authors.

α,α-Dimethylsuccinic anhydride (VI). In a 12-l. flask fitted with a large capacity reflux condenser were mixed 465 g. (8.00 moles) of acetone, 904 g. (8.00 moles) of ethyl cyanoacetate, 480 g. (8.00 moles) of glacial acetic acid, and 632 g. (8.00 moles) of pyridine. The mixture was heated under reflux for forty-five minutes; then 800 ml. of absolute ethanol was added cautiously to the solution. As soon as active refluxing ceased, 548 g. (8.00 moles) of potassium cyanide (95%) was added in small portions as rapidly as the vigorous refluxing (and, in some instances, large amount of frothing) would allow. As some loss of acetone was unavoidable during this operation, 50 g. of additional acetone was added and the mixture was heated under gentle reflux for one hour, then allowed to cool somewhat. To the warm solution was added 3200 ml. of 1:3 hydrochloric acid-water (HOOD!). The layers were separated and the upper organic layer was washed well with water. The aqueous layer and washings were extracted with three 500-ml. portions of ether. The ether was evaporated and the residue was added to the organic layer.

The combined organic materials were heated under reflux with four liters of concentrated hydrochloric acid for six hours. Then 800 ml. of concentrated hydrochloric acid was added and the heating was continued for two hours. Without cooling, about two liters of hydrochloric acid was distilled from the reaction mixture and the resultant solution was chilled in ice. The precipitated solids were collected and the filtrate was evaporated to dryness under reduced pressure, yielding a second crop of solid. The combined solids were extracted eight times with 500-ml. portions of boiling ether. The ethereal solution was dried briefly over sodium sulfate and the ether was removed. The crude α,α-dimethylsuccinic acid (V) was dried by distilling from it 500 ml. of benzene until the distillate collected in a modified Dean-Starke water separator (19) was free from water. The remaining benzene was removed by distillation.

The crude dry acid was heated with 1020 g. (10.00 moles) of acetic anhydride for one hour on the steam-bath. The reaction mixture was distilled under reduced pressure through a 6-in. Vigreux column. The high-boiling fraction was redistilled through a 12-in. helices-packed column. The yield was 623 g. (4.87 moles, 61%), boiling at 102–103° (15 mm.).

In similar experiments involving quantities from one to eight moles, the yields were 53–61%. In several experiments, V was isolated and purified by recrystallization from ether-benzene solution (10), the yield being 53–69%. Conversion of pure V into VI by the above procedure then gave a yield for the one step of 92–97%. In one experiment in which acetyl chloride was used in place of acetic anhydride, the yield was 90% (9, 12).

α,α-Dimethyl-β-carbethoxypropionic acid (VIII). The 623 g. (4.87 moles) of VI and 897 g. (19.5 moles) of absolute ethanol were heated under gentle reflux on the steam bath for four hours. The excess ethanol was evaporated under reduced pressure (water pump) from a flask fitted with a thermometer reaching into the liquid. The temperature was kept below 60° during this process. On chilling in ice, the residue solidified to a moist mush, a mixture of VII and VIII. The crude half-esters were heated with 1.5 l. of low-boiling petroleum ether. The petroleum ether solution was decanted off the undissolved solid through cotton and chilled. Pure VIII separated, the filtrate was returned to the flask, and the process was repeated. Five extractions with the petroleum ether were required to dissolve all of the crude solid. The yield of recrystallized VIII was 627 g. (74%), m.p. 67–68° (lit. m.p. 68° (12)), neutralization equivalent 173.1, calculated for VIII, 174.2.

In similar experiments involving quantities from 0.25 to 4.87 moles, the yields were 72–77%.

The petroleum ether filtrate was evaporated on the steam bath and the residue was heated with 800 ml. of concentrated hydrochloric acid for two hours. The hydrochloric acid was evaporated under reduced pressure and the residue (V) was converted by the above process into VIII. The total yield of VIII was 929 g. (4.19 moles, 86%). In similar experiments involving quantities from 0.5 to 4.87 moles, the total yields were 86–90%.

Ethyl β,β-dimethyllevulinate (X). A mixture of 174 g. (1.00 mole) of VIII and 238 g. (2.00 moles) of pure thionyl chloride was allowed to stand overnight. The excess thionyl chloride was removed under reduced pressure, the flask being heated gently during the process so that a thermometer reaching into the liquid showed no higher than 40°. Two 100-ml. portions of dry thiophene-free benzene were added to the crude acid chloride and evaporated below 40° to sweep out the last traces of thionyl chloride. The crude IX prepared in this manner was used directly in the following reactions.

(A) Over a period of five to ten minutes, 55 g. (0.3 mole) of cadmium chloride (dried in a vacuum oven) was added in small portions to 125 ml. (0.5 mole) of a $4M$ solution of methylmagnesium bromide in ethyl ether, cooled in ice. The mixture was heated under reflux until a negative test was obtained with Michler's ketone. The ether was removed, 200 ml. of dry thiophene-free benzene was added, and about 40 ml. of the benzene was distilled to sweep out the ether. To the cooled solution of dimethylcadmium was added, with vigorous stirring, 0.2 moles of the crude IX (one-fifth of the above preparation) dissolved in 100 ml. of dry benzene. After the addition of the acid chloride was completed, the mixture was heated under reflux for thirty minutes. The mixture was cooled in ice and the organometallic complex was decomposed with ice and $6N$ sulfuric acid. The layers were separated and the aqueous layer was extracted with two 25-ml. portions of benzene. The combined benzene solutions were washed successively with water, 10% aqueous sodium bicarbonate, and more water. After brief drying over sodium sulfate, the benzene was removed, and distillation of the residue under reduced pressure gave 21.4 g. (62%) of X, b.p. 99–100° (15 mm.), n_D^{25} 1.4279, d_4^{25} 0.969.

The semicarbazone of X formed very slowly in dilute ethanol and was recrystallized from the same solvent, m.p. 128.6–129.0°.

Anal. Calc'd for $C_{10}H_{19}N_3O_3$: C, 52.38; H, 8.35; N, 18.33.
Found: C, 52.55; H, 8.47; N, 18.45.

In similar experiments with quantities varying from 0.1 to 0.4 mole the yields of X were 57–62%. When methylmagnesium iodide was used instead of methylmagnesium bromide in the preparation of the dimethylcadmium, the yields were 47–52%. The X prepared in this fashion probably contains a small amount of the diethyl ester of V (15), but is quite satisfactory for preparative purposes.

(B) To a three-necked, 3-l. flask fitted with stirrer, condenser, and dropping funnel were added 29 g. (1.2 moles) of magnesium turnings, 25 ml. (0.424 mole) of absolute ethanol, and 2.5 ml. of carbon tetrachloride. After the vigorous reaction had proceeded for several minutes, 750 ml. of dry ether was added cautiously. A solution of 176 g. (1.20 moles) of freshly distilled diethyl malonate, 100 ml. (1.70 moles) of absolute ethanol, and 125 ml. of dry ether was added as rapidly as the vigorous reaction would allow. The solution was heated under reflux for three hours.

To the pale gray solution was added as rapidly as the refluxing would allow a solution of 1.0 mole of crude IX in 250 ml. of dry ether. The resultant green solution was heated under reflux for thirty minutes. The magnesium complex was decomposed by adding an ice cold solution of 10% sulfuric acid to the cooled ethereal solution. The ether layer was separated and washed well with water. The ether was evaporated on the steam bath and the residue (crude XI) was heated under reflux with 800 ml. of concentrated hydrochloric acid for four hours. The solution was cooled and poured into 1200 ml. of water. The cloudy aqueous solution was extracted five times with 150-ml. portions of ether; the ether extracts were dried over sodium sulfate; and the ether removed.

The residue (crude X and XII) was heated under reflux with 460 g. (10.00 moles) of absolute ethanol containing 14 g. of dry hydrogen chloride for twelve hours. Most of the excess ethanol was distilled and the residue was poured into 1 l. of water. The ester (X) was extracted with four 150-ml. portions of ether; the ether solutions were washed with 5% aqueous sodium bicarbonate and then with water and dried over sodium sulfate. After distillation of the ether, the ester was distilled under reduced pressure through a short Vigreux column. The yield of X was 117–128.5 g. (68–75%), b.p. 98–98.5° (14 mm.), n_D^{25} 1.4245–1.4263. The X prepared in this fashion probably contained a small amount of the diethyl ester of V but was quite satisfactory for preparative purposes.

In one experiment (starting with 1.40 moles of VIII) the crude mixture from the hydrolysis of the intermediate XI was fractionally distilled. Two principal fractions were obtained, b.p. 90–110° (11 mm.) and b.p. 115–120° (4 mm.). The lower-boiling fraction was washed with 5% aqueous potassium carbonate and with water, extracted with ether, dried over potassium carbonate, and, after evaporation of the ether, distilled under reduced pressure through a short Vigreux column. The product, 56 g. (23%), b.p. 96–97° (12 mm.), n_D^{25} 1.4276, d_4^{25} 0.975, M_D^{25} 45.40 (calc'd for X, 45.44), gave a semicarbazone melting at 129.6–130.0°, mixed m.p. with semicarbazone of X prepared by procedure A above, 129.5–130.0°.

Redistillation of the higher boiling fraction gave 115 g. (58%) of XII, b.p. 102° (2 mm.), n_D^{25} 1.4446, d_4^{25} 1.090.

*Anal.** Calc'd for $C_7H_{12}O_3$: C, 58.30; H, 8.39.
Found: C, 58.78; H, 7.89.

The semicarbazone of XII formed rapidly in aqueous solution, m.p. 188.5–189.0° (from water).

*Anal.** Calc'd for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.52; N, 20.88.
Found: C, 47.97; H, 7.45; N, 21.12.

Esterification of the acid (80 g.) in the manner described above gave 85 g. (90%) of X, b.p. 97° (11 mm.), n_D^{25} 1.4263.

Anal. Calc'd for $C_9H_{16}O_3$: C, 62.77; H, 9.37.
Found: C, 62.48; H, 9.07.

δ-Carbethoxy-β,β,γ-trimethyl-γ-valerolactone (XIV). To a three-necked, 3-l. flask fitted with a stirrer, reflux condenser, and dropping funnel were added 70 g. (1.08 moles) of freshly sandpapered zinc foil, a few crystals of iodine, and 150 ml. of a solution of 172 g. (1.00 mole) of X, 200 g. (1.20 moles) of ethyl bromoacetate, 350 ml. of dry toluene, and 400 ml. of dry thiophene-free benzene. The flask was heated to initiate the reaction, which was quite vigorous. The remainder of the solution was added over a period of about one hour with application of sufficient external heating to maintain steady reflux. After the addition of the reactants, the solution was heated under reflux for one hour. The reaction mixture was poured over about 200 g. of crushed ice and the zinc complex was decomposed with 10% sulfuric acid. The aqueous layer was extracted with three 100-ml. portions of benzene. The benzene-toluene solution was filtered through a thin layer of sodium sulfate and the benzene and toluene were removed under reduced pressure. The residue was distilled from a Claisen flask. Three fractions were taken, 70–110° (11 mm.), 90–110° (1 mm.), and 110–150° (1 mm.). Redistillation of the low-boiling fraction through a short Vigreux column gave 51 g. (30%) of recovered X. Redistillation of the two higher-boiling fractions gave 112 g. (50%, 71% based on X used in reaction) of XIV, b.p. 132–135° (1 mm.), n_D^{25} 1.4573–1.4582, d_4^{25} 1.080–1.088, M_D^{25} 53.76–54.15 (calc'd for XIV, 53.96 (27)).

*Anal.** Calc'd for $C_{11}H_{18}O_4$: C, 61.65; H, 8.47.
Found: C, 61.25, 61.42; H, 8.15, 8.08.

In similar experiments involving quantities from 0.2 to 1.0 mole of X, the yields of XIV were 50–54% with a recovery of 30–38% of X. The recovered X could be treated with additional zinc and ethyl bromoacetate, but the yields of XIV were lower (36–43%) indicating that the recovered X contained an impurity not separated by distillation alone The total yield of XIV was 62–69%.

3,3,4-Trimethyl-2-hexene-1,6-dioic acid (XVI). (A) Eighteen grams (0.08 mole) of XIV was heated under reflux with 36 ml. (0.5 mole) of thionyl chloride on the steam bath for three hours. The cooled solution was added to 100 ml. of absolute ethanol saturated at 0° with dry hydrogen chloride. The solution was stirred for 15 minutes, then the excess alcohol was distilled off at atmospheric pressure. The residue was distilled under reduced pressure, using the water pump until the boiling point rose rapidly to 80° at 11 mm. then switching to the oil pump. All of the distillate collected came over at 106–110° (1 mm.). The product was redistilled to remove a small amount of yellow-orange material, giving 17 g. (88%) of the unsaturated ester (XV), b.p. 100–101° (1 mm.), n_D^{25} 1.4565, d_4^{25} 1.003. The product was contaminated with a small amount of sulfur-containing impurity and appeared to alter on standing. It was found advisable to proceed immediately to the hydrolysis step.

Thirteen grams (0.054 mole) of the product (XV) was heated under reflux with a solution prepared from 8.0 (0.20 mole) of sodium hydroxide, 24 ml. of water, and 12 ml. of ethanol for 1.5 hours. The solution was cooled in ice, made acid to Congo Red with hydrochloric acid, and cooled to 5°. A pale yellow oil separated which solidified to a pale cream solid during the cooling process. The solid was dried over potassium hydroxide *in vacuo,* and recrystallized from benzene, giving 9.0 g. (90%) of a white crystalline solid (XVI), m.p. 137.5–138.1°, neutralization equivalent 93.2 (calc'd for XVI, 93.1).

*Anal.** Calc'd for $C_9H_{14}O_4$: C, 58.05; H, 7.58.
Found: C, 58.35; H, 7.53.

In similar experiments involving quantities from 0.08 to 0.4 mole the yields were 74–88%, the higher yields being obtained when a large excess of thionyl chloride was used. When approximately the theoretical amount (22) of thionyl chloride was used, some lactone (XIV) was recovered (10–18%); with the large excess of thionyl chloride no appreciable amount of lactone was detected in the product. When the alcohol was omitted from the hydrolysis mixture, the time for complete hydrolysis was about five hours.

(B) Fifteen grams (0.068 mole) of the same batch of lactone (XIV) as used in the experiment described in (A) above was heated under reflux with 8.4 g. (0.21 mole) of sodium hydroxide, 30 ml. of water, and 15 ml. of ethanol for 1.5 hours. The cooled solution was made acid to Congo Red with hydrochloric acid and chilled in ice. The solid that formed was purified as above, giving 7.0 g. (56%) of white crystalline solid, m.p. 137.5–138.1°, mixed m.p. with the XVI from (A) the same.

The filtrate from the reaction mixture was extracted with three 20-ml. portions of ether. The ether was evaporated on the steam bath and the residue was dried by warming under reduced pressure for twelve hours, leaving 5.7 g. of a viscous, yellow liquid.

In similar experiments with 0.02 to 0.25 mole of XIV, the yield of XVI was 55–60%; the weight of the viscous liquid obtained was about 80–90% of the XVI obtained. Omission of the alcohol from the hydrolysis mixture did not increase the time required for complete hydrolysis of the XIV; however, the reaction proceeded more smoothly and without violence in aqueous alcohol and less so in aqueous solution alone.

The viscous liquid froze in Dry Ice-acetone to a glassy solid. In benzene solution it deposited a small amount of XVI but no other product came out. Addition of petroleum ether to the benzene brought the liquid out of solution. The liquid did not absorb any appreciable amount of hydrogen in the presence of platinum oxide, even after prolonged treatment with Raney nickel and hydrogen (at room temperature and at 80°) to remove catalyst poisons. Attempted distillation of the liquid caused considerable decomposition. The liquid did not decolorize bromine in carbon tetrachloride.

Treatment of 16.5 g. (0.09 mole, calculated for XVI, a lactonic acid corresponding to XIV, or an isomer of either) of the liquid acid with 36 ml. (0.5 mole) of thionyl chloride followed by 100 ml. of ethanol saturated with hydrogen chloride at 0° and subsequent distillation of the reaction mixture, as described in (A) above, gave 13 g. (61%) of XV, b.p. 101–102° (1 mm.), n_D^{25} 1.4555, d_4^{25} 1.001. Hydrolysis of the product gave 8.0 (80%) of XVI, m.p. 137.5–138.2°.

β,β,γ-Trimethyladipic acid (XVII). Hydrogenation of 18.6 g. (0.1 mole) of XVI in 125 ml. of ethanol in the presence of 0.1 g. of platinum oxide was complete in a short time (maximum: forty-five minutes). The product (XVII) was recovered by evaporation of the alcohol and was recrystallized from benzene or a small amount of ethanol. The yield was 16.2–17.8 g. (86–95%) of a white crystalline solid, m.p. 126.5–127.5°.

Anal. Calc'd for $C_9H_{16}O_4$: C, 57.44; H, 8.57.
Found: C, 57.43; H, 8.45.

dl-3,3,4-Trimethylcyclopentanone (III). Twenty-one grams (0.112 mole) of XVII was mixed with 1.82 g. (0.158 mole) of manganous carbonate (4) in a small distilling flask. The mixture was heated at 280–300° in an air bath until no more liquid distilled over. The product was salted out with potassium carbonate, separated from the aqueous layer, dried over potassium carbonate, and distilled. The yield of _dl_-III was 13.3 g. (95%), b.p. 172–173° (740 mm.), n_D^{25} 1.4378, d_4^{25} 0.882.

_Anal._* Calc'd for $C_8H_{14}O$: C, 76.13; H, 11.18.
Found: C, 76.53; H, 11.09.

The following derivatives of _dl_-III were prepared as described by Buchman and Sargent (4). _Semicarbazone_ of _dl_-III, m.p. 213.0–213.5° (from ethanol).

Anal. Calc'd for $C_9H_{17}N_3O$: C, 58.99; H, 9.35; N, 22.93.
Found: C, 59.35; H, 9.36; N, 23.01.

Oxime of _dl_-III, m.p. 99.5–100.0° (from very dilute ethanol)

Anal. Calc'd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92.
Found: C, 67.70; H, 10.38; 10.18.

Bis-p-nitrobenzal derivative of _dl_-III, α-form, orange yellow needles, m.p. 205.0–205.5° (from benzene)

_Anal._* Calc'd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14.
Found: C, 67.63; H, 5.36; N, 7.00.

Bis-p-nitrobenzal derivative of _dl_-III, β-form, pale yellow rhombs, m.p. 202.8–203.2° (from benzene)

_Anal._* Calc'd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14.
Found: C, 67.50; H, 5.25; N, 6.89.

SUMMARY

Ethyl β,β-dimethyllevulinate undergoes the Reformatsky reaction with ethyl bromoacetate to form δ-carbethoxy-β,β,γ-trimethyl-γ-valerolactone. The latter is converted by alkaline hydrolysis and dehydration or by successive treatment with thionyl chloride and alcoholic hydrogen chloride followed by thermal dehydrohalogenation and hydrolysis to 3,3,4-trimethyl-2-hexene-1,6-dioic acid. Catalytic hydrogenation of the unsaturated acid to β,β,γ-trimethyladipic acid and cyclization of the latter affords a new synthetic route to _dl_-3,3,4-trimethylcyclopentanone. The properties of _dl_-3,3,4-trimethylcyclopentanone have been found to be in agreement with those reported by Buchman and Sargent for their synthetic ketone but not with those reported by Mukherji for her synthetic ketone nor with those reported by von Braun for a $C_8H_{14}O$ ketone from naphthenic acid degradations.

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