chromatography,[25] $[\alpha]^{25}D$ −24° (*c* 1.00, chloroform). Treatment of the product with alkali gave a substance which showed λ_{max}^{EtOH} 325 mμ and $\lambda_{max}^{0.1N\ NaOH}$ 377 mμ, characteristic of the diosphenol derived from 16-dehydroprotoverine derivatives.[16]

Sodium Borohydride Reduction of 16-Dehydroprotoveratrine B 3′-Tiglate (XI).—A solution of 16-dehydroprotoveratrine B 3′-tiglate (XI, 0.547 g., $[\alpha]^{25}D$ −24°) in *t*-butyl alcohol (50 ml.) was treated with sodium borohydride (0.126 g.). The mixture was allowed to stand, with occasional shaking, at room temperature for 30 min. The solution was acidified with acetic acid and evaporated nearly to dryness under reduced pressure. The residue was dissolved in water, made basic with dilute ammonium hydroxide, and extracted thoroughly with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was crystallized from ether (0.212 g.). Paper chromatography[26] showed that the crystalline product was inhomogeneous; a principal product with expected R_f was contaminated with other materials (probably partially hydrolyzed) with much lower R_f. Furthermore, the mother liquors contained only a mixture of the low R_f products. Chromatography of the crystalline mixture on Merck acid-washed alumina (42 g.) yielded to 50 to 80% chloroform–benzene, to chloroform, and to 0.5 to 1% methanol in chloroform a resin with R_f identical to that of protoveratrine B 3′-tiglate (X). Crystallization from acetone–ether yielded prisms (0.145 g.), m.p. 154–156°, with decomposition at *ca.* 173°; $[\alpha]^{29}D$ +10° (*c* 1.70, chloroform).

Anal. Calcd. for $C_{46}H_{69}O_{16}N$: C, 61.95; H, 7.74. Found: C, 61.95; H, 7.76. The melting point was not depressed by admixture of an authentic sample of protoveratrine B 3′-tiglate which had been crystallized from the same solvent, and the infrared spectra of the respective samples in chloroform solution were identical.

Osmium Tetroxide-Periodic Acid Cleavage of Protoveratrine B 3′-Tiglate (X).—To a stirred solution of protoveratrine B 3′-tiglate (X, 0.208 g.) in dioxane (30 ml.) and water (10 ml.) was added osmium tetroxide (15 mg.). After 10 min., a black color developed, whereupon periodic acid (0.232 g.) was added and the solution was stirred for 10 hr. at room temperature. The reaction mixture was treated with 0.1 *N* sodium arsenite solution containing a crystal of potassium iodide to pH 8.7, and stirred for 10 min. Extraction with chloroform and work-up by the usual procedure yielded a resin which was crystallized from acetone–ether to give prisms (0.113 g., 60%), m.p. 267–270° dec. The infrared spectrum in chloroform solution and the paper chromatographic behavior[26] were identical to those of an authentic sample of protoveratrine B.

(26) The paper chromatographic system was that of J. Levine and H. Fischbach [*J. Am. Pharm. Assoc.*, **44**, 543 (1955)]; *n*-butyl acetate–*n*-butanol–formic acid (25:5:1 by volume).

Chemistry of Dimethylketene Dimer. V. Reactions Involving Ester Anions[1]

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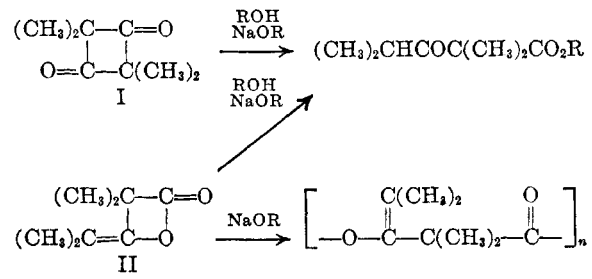
In the presence of a catalytic amount of sodium methoxide, the dimethylketene dimers (I and II) are disproportionated above 100° to the cyclic trimer, hexamethyl-1,3,5-cyclohexanetrione (V). The reaction involves the formation and acylation of the sodium enolate of methyl 2,2,4-trimethyl-3-oxovalerate. Various modes of preparing, alkylating, and acylating this sodium enolate are described.

The cleavage of tetramethyl-1,3-cyclobutanedione (dimethylketene dimer, I) by alcohols is catalyzed by basic reagents and leads to esters of 2,2,4-trimethyl-3-oxovaleric acid.[2] The β-lactone dimer of dimethylketene (II) is a more reactive acylating reagent than dimer I, but it also reacts sluggishly with alcohols unless a catalyst, preferably a base, is present. In the absence of active hydrogen compounds, the lactone dimer II, heated at moderate temperatures with sodium methoxide, is converted to a polyester; under the same conditions, dimer I does not react.[1]



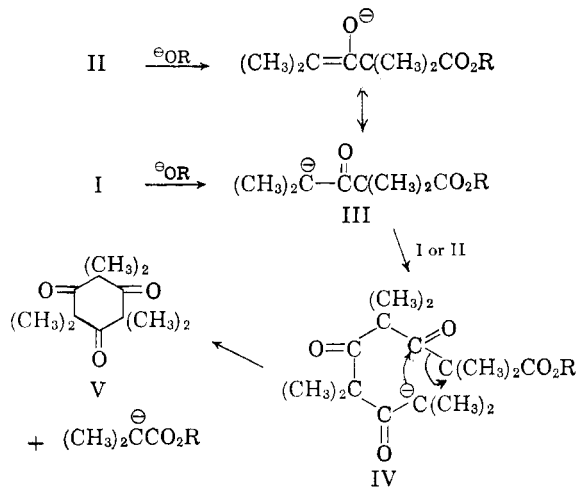
When the reaction of the normal dimer I with sodium methoxide is forced by the use of higher temperatures, an exothermic disproportionation reaction takes place, and a high yield of the cyclic trimer, hexamethyl-1,3,5-cyclohexanetrione (V), is obtained.[3] Under these same conditions, the lactone dimer II, instead of polymerizing, is also converted to the cyclic trimer. It is evident that the two dimers react with sodium methoxide to form a common intermediate, the sodium enolate of methyl 2,2,4-trimethyl-3-oxovalerate (III).[4] The disproportionation of a dimethylketene dimer then involves the cleavage of another mole of dimer by the enolate III to generate the triketo ester anion IV. The cyclic trimer V is formed by an intramolecular attack of the nucleophilic center on the β-carbonyl group, with elimination of the methyl isobutyrate anion.

(1) Paper IV, R. H. Hasek, R. Donald Clark, E. U. Elam, and J. C. Martin, *J. Org. Chem.*, **27**, 60 (1962).

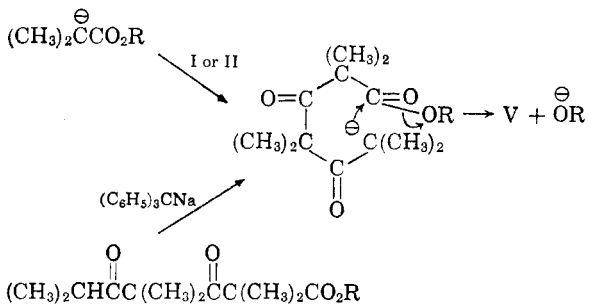
(2) R. H. Hasek, E. U. Elam, J. C. Martin, and R. G. Nations, *J. Org. Chem.*, **26**, 700 (1961).

(3) J. L. E. Erickson and G. C. Kitchens, *J. Org. Chem.*, **27**, 460 (1962).

(4) C. R. Hauser and W. B. Renfrow, Jr., *J. Am. Chem. Soc.*, **59**, 1824 (1937).

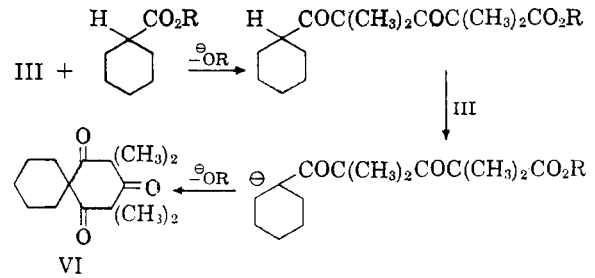


By an analogous mechanism, the by-product methyl isobutyrate anion reacts with more dimer to form the trimer and regenerate the methoxide ion. The preparation of the trimer has been reported *via* the same intermediate diketo ester anion, prepared by action of tritylsodium on the diketo ester.[5]



Although this mechanism is the logical path of the disproportionation reaction, it is an oversimplification of the actual state of the reaction system. At moderate temperatures (<80°), III does not react with the dione dimer I, but only with the more reactive lactone dimer II. In this latter case, the preferred mode of action is an *O*-acylation of III, and the product does not undergo cyclization; instead, the dimer continues to *O*-acylate the growing ester anion to the eventual formation of a polyester.[1] The formation of the cyclic trimer at higher temperatures is evidence that *C*-acylation of III (by either dimer) has become appreciable. Continued *C*-acylation to the production of a polyketone is nullified by preferential cyclization to a six-membered ring.[6] Actually, the disproportionation of these ketene dimers undoubtedly involves the formation and cleavage of a complex mixture of keto ester anions, and these equilibria are displaced by production of the thermodynamically favored cyclic trimer.

According to the above mechanisms, the addition of a dialkylacetic ester to the disproportionation reaction should lead to products which incorporate the ester. This was found to be the case; when the disproportionation of I was carried out in methyl cyclohexanecarboxylate, a mixture of high-boiling products was obtained from which the spiro ketone VI was isolated. The mechanism shown for its formation is only one of several possible reaction paths.



The addition of conjugate acids—*i.e.*, esters, alcohols—in the disproportionation reaction increases the complexity of the reaction system, and syntheses carried out in this fashion are not likely to be very specific. The numerous equilibrium reactions involved may be divided into two types: acylation-cleavage reactions and acid-base exchange. If the dimethylketene moiety, —C(CH$_3$)$_2$CO—, is represented by *D*—*e.g.*, (CH$_3$)$_2$CHCOC(CH$_3$)$_2$CO$_2$R = H*DD*OR—some of the equilibria may be formulated in the following manner.

$$D_2\ (\text{I or II}) + \overset{\ominus}{\text{O}}\text{R} \overset{a}{\rightleftharpoons} \overset{\ominus}{D}D\text{OR (III)}$$

$$D_2 + \overset{\ominus}{D}D\text{OR} \overset{b}{\rightleftharpoons} \overset{\ominus}{D}DDD\text{OR (IV)} \overset{c}{\rightleftharpoons} D_3\ (\text{V}) + \overset{\ominus}{D}\text{OR}$$

$$D_2 + \overset{\ominus}{D}\text{OR} \overset{d}{\rightleftharpoons} \overset{\ominus}{D}DD\text{OR} \overset{e}{\rightleftharpoons} D_3 + \overset{\ominus}{\text{O}}\text{R}$$

$$\text{ROH} + \overset{\ominus}{D}\text{OR} \overset{f}{\rightleftharpoons} H D\text{OR} + \overset{\ominus}{\text{O}}\text{R}$$

$$\text{ROH} + \overset{\ominus}{D}D\text{OR} \overset{g}{\rightleftharpoons} HDD\text{OR} + \overset{\ominus}{\text{O}}\text{R} \overset{h}{\rightleftharpoons} H D\text{OR} + \overset{\ominus}{D}\text{OR}$$

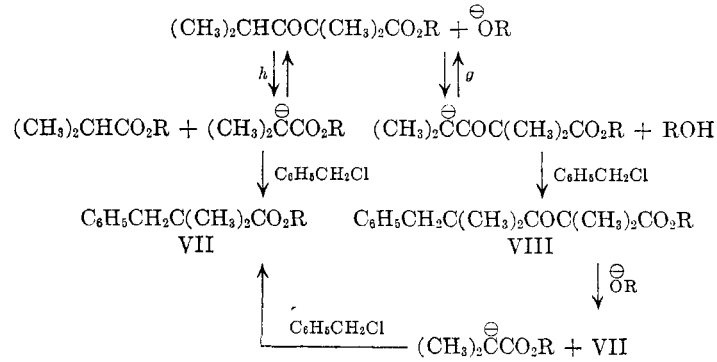
$$\text{ROH} + \overset{\ominus}{D}DD\text{OR} \overset{i}{\rightleftharpoons} HDDD\text{OR} + \overset{\ominus}{\text{O}}\text{R} \overset{j}{\rightleftharpoons} H D\text{OR} + \overset{\ominus}{D}D\text{OR}$$

$$H D\text{OR} + \overset{\ominus}{D}D\text{OR} \overset{k}{\rightleftharpoons} HDD\text{OR} + \overset{\ominus}{D}\text{OR}$$

In essence, the disproportionation reaction involves the equilibria *a–e;* they are displaced by preferential formation of the cyclic trimer D_3 (V). Since the alkoxide anion is regenerated, a catalytic amount suffices to promote the conversion of the dimethylketene dimers to the trimer. By addition

(5) B. E. Hudson, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **61**, 3567 (1939).

(6) The formation of this trimer in the polymerization of monomeric dimethylketene over aluminum bromide has been described. The polymerization normally leads to a polyketone, but with high catalyst concentrations the cyclic trimer can be the major product. [G. F. Pregaglia, G. Mazzanti, and M. Binaghi, *Makromol. Chem.*, **48**, 234 (1961)].



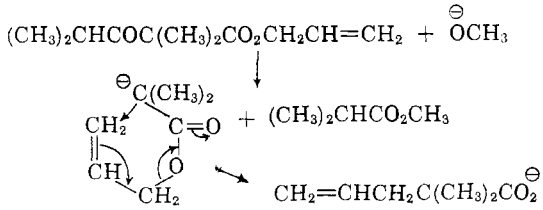
of a stoichiometric amount of alkoxide and selection of the proper reaction conditions, the dimers can be converted to the enolate III.[7] The sodium derivative can be isolated as a light buff powder, stable at room temperature in the absence of air or moisture.

The addition of excess sodium methoxide to a dimethylketene dimer, in the presence of a little methyl isobutyrate, did not lead to the sodium enolate of this ester. The equilibria k and h lie far to the left, and the net reaction is likewise in this direction.

$$(CH_3)_2\overset{\ominus}{C}COC(CH_3)_2CO_2R + \overset{\ominus}{O}R \rightleftharpoons 2(CH_3)_2\overset{\ominus}{C}CO_2R$$

In effect, this equation simply states that the isobutyrate ester anion is unstable and dissociates to the two more weakly basic anions on the left. The trimethyloxovalerate ester anion III is unstable in the same sense, but only at higher temperatures. The solid sodium derivative can be kept in a dry, inert atmosphere for months with a slight decrease in purity. It is degraded rapidly at 100°.

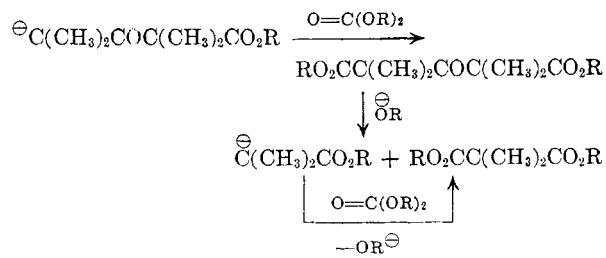
The formation of the isobutyrate ester anion by h would appear to be very unfavorable, but there is ample evidence for this equilibrium. The cleavage of β-keto esters, especially those with two substituents on the α-carbon, by alcoholic sodium alkoxides is well known.[8] The equilibrium is displaced by neutralization of the strongly basic ester anion in the relatively acidic solvent. The equilibrium can also be shifted in an inert solvent. Allyl 2,2,4-trimethyl-3-oxovalerate was cleaved by



sodium methoxide to form methyl isobutyrate and the sodium salt of 2,2-dimethyl-4-pentenoic acid; the latter is the product of a Claisen-type rearrangement of the allyl isobutyrate anion.

Displacement of equilibrium k to the right also can be accomplished by removal of the isobutyrate ester by distillation. A stoichiometric mixture of methyl trimethyloxovalerate and sodium methoxide evolved the theoretical amount of methyl isobutyrate, but the residual methyl isobutyrate anion dissociated too rapidly to accumulate in appreciable concentration. If an alkylating agent was present during the displacement, the ester anion was trapped. Alkylation of the keto ester anion III, formed by reversal of reactions g or k, also occurred. Undoubtedly, the trialkylacetic ester (VII) also was formed by cleavage of the completely alkylated acetoacetic ester (VIII), and not solely by the alkylation of a transient methyl isobutyrate anion; however, cleavage of the keto ester VIII in the presence of the alkylating agent gave VII in yields which demonstrated unequivocally the trapping of the methyl isobutyrate anion.

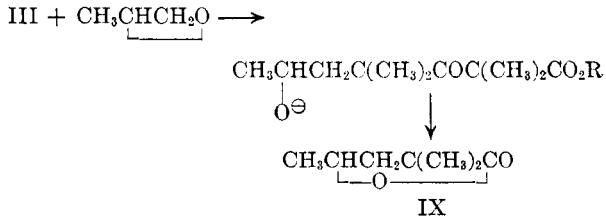
Acylation of the keto ester anion III (ethyl ester) with an excess of ethyl carbonate led to diethyl dimethylmalonate, produced both by cleavage of the intermediate 2,2,4,4-tetramethyl-3-oxoglutaric ester and by acylation of the resulting isobutyrate anion.



The ease of cleavage of the β-keto esters derived from III is governed by several factors. Alkylation of III with propylene oxide gave the γ-lactone (IX) expected from the alkylation of an isobutyrate ester anion. Since an intramolecular attack by an alkoxide ion is involved, the result is not too surprising.

(7) Under these conditions, the formulation of the reaction as an equilibrium (a) is not obvious; however, the reversibility of g and a was demonstrated by the formation of the β-lactone dimer II and the trimer V from destructive distillation of a trimethyloxovaleric ester over sodium acetate.[1]

(8) C. R. Hauser and B. E. Hudson, Jr., *Org. Reactions*, 269 (1942).



In the base-catalyzed reaction of tetramethyl-1,3-cyclobutanedione (I) with excess *tert*-butyl alcohol, substantial cleavage resulted when sodium methoxide was used as the catalyst. The major product was *tert*-butyl isobutyrate. When the catalyst was sodium hydride, extensive cleavage did not take place and *tert*-butyl 2,2,4-trimethyl-3-oxovalerate was obtained in good yield. The *tert*-butoxide anion, generated from the sodium hydride, is thus inactive in the cleavage reaction, presumably for steric reasons.

The preparation and reactions of isobutyrate ester anions have been studied extensively by Hauser and his students.[9] The major inconvenience in their work was the necessity of using tritylsodium as the basic reagent. The reaction of the dimethylketene dimers with sodium alkoxides provides a convenient entry into this ester anion chemistry. Although it does not lead directly to isobutyrate ester anions, the desired derivatives often can be obtained by suitable displacement of the numerous equilibria involved. In this regard, it must be said that our knowledge of these systems is far from complete.

Experimental

Hexamethyl-1,3,5-cyclohexanetrione (V). A. From Tetramethyl-1,3-cyclobutanedione (I).—A mixture of 1000 g. of I, 1000 ml. of xylene, and 10 g. of sodium methoxide was heated to 85–90°. When the exothermic reaction started, heating was discontinued; the mixture refluxed for about 45 min. After the reaction subsided, external heating was resumed; the mixture was refluxed for 2 hr. and then distilled. After removal of the xylene, 881 g. (88%) of hexamethyl-1,3,5-cyclohexanetrione was received, b.p. 245–247°. The solid product, m.p. 78–80°, was recrystallized from ethyl alcohol to give colorless needles, m.p. 80°.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.5; H, 8.6; mol. wt., 210. Found: C, 68.3; H, 8.7; mol. wt. (ebullioscopic in benzene), 227.

B. From 3-Hydroxy-2,2,4-trimethyl-3-pentenoic Acid β-Lactone (II).—A mixture of 316 g. of II and 5.2 g. of sodium methoxide was heated rapidly. When the temperature reached 90°, an exothermic reaction began and the temperature rose to 230° without further heating. When the reaction began to subside, heating was resumed and the mixture was refluxed for 1 hr. The product was cooled to 100°, poured into water, stirred with a Waring Blendor to pulverize the solid material, and filtered. The solid was washed with water and dried to give 274 g. (87%) of hexamethyl-1,3,5-cyclohexanetrione, m.p. 76–79°. After one recrystallization from ethyl alcohol, the product (212 g., 67%) melted at 79–80°. The melting point of a mixture with an authentic sample was not depressed.

2,2,4,4-Tetramethylspiro[5.5]undecane-1,3,5-trione (VI).—A mixture of 320 g. (2.3 moles) of methyl cyclohexanecarboxylate and 140 g. (1.0 mole) of 2,2,4-trimethyl-3-hydroxy-3-pentenoic acid β-lactone was heated to reflux, and 6.0 g. of sodium methoxide was added in four portions. The vigorous reaction after each addition was allowed to subside before addition of the next portion of catalyst. The mixture was then refluxed for 5 min. and distilled rapidly through a short Vigreux column. Four fractions were taken; the last two contained solid product. The solid filtered from the third fraction was crude hexamethyl-1,3,5-cyclohexanetrione (V, 38 g., 27%); after recrystallization from ethyl alcohol, it melted at 78–79.5°, and in a mixture with authentic V, at 78–80°.

The solid from the fourth fraction was crude VI (18 g., 7%), m.p. 95–102°. Recrystallization from ethyl alcohol and then from ligroin raised the melting point to 104–105°.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 72.0; H, 8.9; mol. wt., 250. Found: C, 72.2; H, 8.8; mol. wt. (ebullioscopic in benzene), 252.

Preparation of the Sodium Enolate of Methyl 2,2,4-Trimethyl-3-oxovalerate.—A mixture of 113 g. (2.0 moles) of 95% sodium methoxide and 1 l. of tetrahydrofuran was heated to reflux under nitrogen. Heating was stopped and the mixture was stirred while 280 g. (2.0 moles) of 2,2,4-trimethyl-3-hydroxy-3-pentenoic acid β-lactone was added over a period of 25 min. The mixture was then refluxed for 15 min. The solvent was evaporated by a stream of dry nitrogen at such a rate that, although some heat was applied, the reaction mixture remained below room temperature. When solid material separated, the pressure was reduced to 100–300 mm. Drying was continued for 4 days, with the pressure eventually reduced to 10–25 mm. The sodium enolate, a light yellow powder, weighed 388 g. (98%). A sample was quenched in water and examined by gas chromatography (Carbowax 20M on Chromosorb-P). The chromatogram contained one major peak corresponding to methyl 2,2,4-trimethyl-3-oxovalerate; insignificant amounts of impurities were present.

A sample of the sodium enolate, stored under nitrogen at room temperature for 16 months, was assayed in the same manner. The chromatogram showed a slight decrease in purity of the hydrolyzed product (80–85% methyl 2,2,4-trimethyl-3-oxovalerate, area percent, uncorrected).

Alkylation and Acylation of the Sodium Enolate of Methyl 2,2,4-Trimethyl-3-oxovalerate (III).—It was not necessary to isolate the sodium enolate III prior to alkylation or acylation. Where reactive alkylation and acylation reagents were involved, the sodium enolate was prepared first, but if the reagents were fairly unreactive toward sodium methoxide, the enolate could be prepared *in situ*. The following experiments illustrate various modes of operation. Results are summarized in Table I.

A. Dimethyl 2,2,4,4-Tetramethyl-3-oxoglutarate.—A solution of the sodium enolate of methyl 2,2,4-trimethyl-3-oxovalerate was prepared as previously described by addition of 140 g. (1.0 mole) of 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone to 56 g. of 95% sodium methoxide in 500 ml. of tetrahydrofuran. This solution was added over a period of 25 min. to a solution of 94.5 g. (1.0 mole) of methyl chloroformate in 250 ml. of tetrahydrofuran. The temperature was kept below 50° by intermittent cooling. After the addition was complete, the mixture was refluxed for 15 min., acidified with 10 ml. of acetic acid, and filtered. The solvent was stripped and the residue was distilled through a 1.8 × 25-cm. column packed with protruded packing (Scientific Development Co., State College, Pennsylvania). Dimethyl 2,2,4,4-tetramethyl-3-oxoglutarate (145 g., 63%) was received, b.p. 97–98° (3 mm.), $n^{20}D$ 1.4470–1.4480.

B. Methyl 2,2,4,4-Tetramethyl-3-oxo-5-phenylvalerate.—A mixture of 140 g. (1.0 mole) of tetramethyl-1,3-cyclobutanedione, 57 g. (1.0 mole) of 95% sodium methoxide, 126.6 g. (1.0 mole) of benzyl chloride, and 150 ml. of toluene was stirred and heated to 57°. At this point, a mildly exothermic reaction started and was controlled at 56° for 3 hr.

(9) For a review, see ref. 8.

TABLE I

METHYL 4-ALKYL- AND 4-ACYL-2,2,4-TRIMETHYL-3-OXOVALERATES

$RC(CH_3)_2COC(CH_3)_2CO_2CH_3$

R	B.p.	$n^{20}D$	Yield, %	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Mol. wt.[b]— Calcd.	Found
$C_6H_5CH_2$—	39.5–41.5[a]		55	73.3	73.1	8.5	8.5	262	262[c]
p-$C_6H_4(CH_2—)_2$	135.5–138[a]		35	69.9	69.8	8.6	8.6	447	448[d]
CH_3CO—	59–60 (0.5 mm.)	1.4490	45	61.7	61.3	8.5	8.5	214	220
$C_6H_{11}CO$—	125 (0.4 mm.)	1.4730	61	68.1	67.7	9.3	9.3	282	278
CH_3O_2C—	97–98 (3 mm.)	1.4475	63	57.4	57.7	7.9	8.0	230	233
CH_3O_2CCO—	138–142 (5 mm.) 91–92[a]		27	55.8	55.7	7.0	7.1	258	245

[a] Melting point. [b] Ebullioscopic in benzene. [c] Sapon. equiv., 265. [d] Sapon. equiv., 220.

The mixture was then slowly heated to reflux (1.5 hr.), refluxed for 1 hr., allowed to stand overnight, poured into ice water, and extracted with benzene. The extracts were dried over magnesium sulfate and distilled under vacuum to a base temperature of 130° (40 mm.). The residue was dissolved in 4 l. of hexane, and the solution was chilled in Dry Ice. The crystalline solid (143 g., 55%), m.p. 34–37.5°, was recovered and recrystallized twice from hexane and twice from methanol (the melting point of 39.5–41.5° was unchanged by the last three recrystallizations) to give pure methyl 2,2,4,4-tetramethyl-3-oxo-5-phenylvalerate.

A mixture of 23 g. of methyl 2,2,4,4-tetramethyl-3-oxo-5-phenylvalerate, 60 ml. of glacial acetic acid, 20 ml. of concd. sulfuric acid, and 20 ml. of water was refluxed with stirring for 8 hr. The reaction mixture was cooled, diluted with 200 ml. of water, and made basic to phenolphthalein with 20% aqueous sodium hydroxide solution. The mixture was extracted three times with ether, the extracts were dried over magnesium sulfate and the ether was stripped by distillation. The residue was distilled under reduced pressure through a 1.8 × 25-cm. packed column. The 2,4,4-trimethyl-5-phenyl-3-pentanone, b.p. 103–104° (3 mm.), $n^{20}D$ 1.4990, amounted to 11 g. (62%); it crystallized on standing. A center cut, m.p. 27.5–28.5°, was analyzed.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.3; H, 9.87; mol. wt., 204. Found: C, 82.3; H, 9.86; mol. wt. (ebullioscopic in benzene), 207.

The 2,4-dinitrophenylhydrazone was prepared by the conventional procedure, except that prolonged heating was required. The derivative was recrystallized from ethyl alcohol to a constant melting point of 175–176°.

Anal. Calcd. for $C_{20}H_{24}N_4O_4$: N, 14.6. Found: N, 14.5.

C. 4-Hydroxy-2,2-dimethylvaleric Acid γ-Lactone (IX).—A mixture of 70 g. (0.5 mole) of tetramethyl-1,3-cyclobutanedione, 35.5 g. (0.6 mole) of 95% sodium methoxide, and 275 ml. of benzene was stirred and heated under a reflux condenser protected with a drying tube. The temperature was raised to 70° over a period of 35 min., held at 70–75° for 30 min., brought to reflux during 15 min., and refluxed for 30 min. Stirring was continued while the temperature was allowed to fall to room temperature (2 hr.). Propylene oxide (58 g., 1.0 mole) was added at 21–24° over a period of 35 min. The mixture was then heated and refluxed for 80 min. Heating was stopped; the mixture was stirred overnight, then poured into ice water. The aqueous layer was separated and extracted with two 100-ml. portions of benzene. The organic layer and the extracts were combined, dried over magnesium sulfate, and distilled. A fraction, b.p. 75–86° (10 mm.) contained a solid which was recrystallized from hexane to give 26 g. of product, m.p. 47–50.5°.

The aqueous layer was acidified with sulfuric acid and distilled; the oily solid which separated from the distillate was recrystallized from hexane to give 23 g. of product, m.p. 45–50°. The combined yield of 49 g. of 4-hydroxy-2,2-dimethylvaleric acid γ-lactone represented a 38% yield. An analytical sample, prepared by recrystallization once more from hexane and then twice from ether, melted at 49–50.5°; a value of 52° has been reported.[10]

Anal. Calcd. for $C_7H_{22}O_2$: C, 65.6; H, 9.4; mol. wt., 128; sapon. equiv., 128.2. Found: C, 65.6; H, 9.5; mol. wt. (cryoscopic in benzene), 135; sapon. equiv., 128.4.

D. Dimethyl α,α,α′α′,γ,γ,γ′,γ′-Octamethyl-β,β′-dioxo-p-benzenedivalerate.—A suspension of the sodium enolate of methyl 2,2,4-trimethyl-3-oxovalerate was prepared as described in the preceding experiment. With the suspension at room temperature, 35 g. (0.2 mole) of *p*-xylylene dichloride was added rapidly; the mixture was stirred without heating for 30 min., and then was heated to boiling (30 min.) and refluxed for 30 min. After being cooled to 8°, the mixture was poured into ice water and extracted with 900 ml. of benzene (in three portions). The extracts were dried over sodium sulfate and stripped of solvent by distillation. The yellow solid residue, after being heated at 85–90° under 2 mm. pressure, weighed 87.4 g. (98%) and melted at 102–104°. Recrystallizations from methanol and methyl isobutyrate gave a slightly colored product, m.p. 133–137°. It was finally placed in a Soxhlet thimble on top of a column of granular alumina and extracted with hexane. Colored impurities remained on the alumina. The purified dimethyl octamethyldioxobenzenedivalerate, m.p. 135.5–138°, weighed 30.8 g. (35%).

Formation and Rearrangement of Allyl Isobutyrate Anion.—Allyl 2,2,4-trimethyl-3-oxovalerate was prepared by alkaline-catalyzed alcoholysis of tetramethyl-1,3-cyclobutanedione.[2] Five grams of sodium was dissolved in 1000 g. of allyl alcohol, and 2000 g. of tetramethyl-1,3-cyclobutanedione was added at such a rate that the temperature of the reaction mixture did not exceed 40°. The mixture was then stirred for 2.5 hr., and the catalyst was neutralized with 15 ml. of acetic acid. Distillation through a packed column gave 2029 g. (73% of allyl 2,2,4-trimethyl-3-oxovalerate, b.p. 95–96° (10 mm.), $n^{20}D$ 1.4368–1.4370.

Allyl 2,2,4-trimethyl-3-oxovalerate (198 g., 1.0 mole) was added to a stirred suspension of 57 g. (1.0 mole) of 95% sodium methoxide in 400 ml. of xylene in a flask equipped with a reflux condenser and a thermometer. During 25 min., the temperature rose slowly to 33°; heat was applied until the reaction again became exothermic at 70°. The temperature rose gradually to 120° without further external heating. Volatile products, 90.5 g., b.p. 79–115°, were then removed by distillation; redistillation through a packed column gave 60 g. (59%) of methyl isobutyrate, b.p. 90–92° (730 mm.), $n^{20}D$ 1.3830.

The residual reaction mixture was poured into ice water and acidified with 100 ml. of concd. hydrochloric acid. The organic layer was separated, the aqueous layer was extracted twice with 50-ml. portions of xylene, and the combined materials were dried over magnesium sulfate. Distillation through a packed column gave a low-boiling fraction (from which 10 g. of methyl isobutyrate was recovered) and then 70.5 g. (55%) of 2,2-dimethyl-4-pentenoic acid, b.p. 93–94.5° (9 mm.), $n^{20}D$ 1.4333.[11]

Cleavage of Methyl 2,2,4-Trimethyl-3-oxovalerate with Sodium Methoxide.—A mixture of 172 g. (1 mole) of methyl

(10) R. Anschutz and C. Gillet, *Ann.*, **247**, 107 (1888).

(11) K. C. Brannock, *J. Am. Chem. Soc.*, **81**, 3379 (1959).

2,2,4-trimethyl-3-oxovalerate and 57 g. (1 mole) of 95% sodium methoxide in 1000 ml. of anisole was gradually heated to 140° over a period of 75 min. The mixture was allowed to stand overnight at room temperature. Distillation through a packed column gave 84 g. of methyl isobutyrate, b.p. 91.5–95° (730 mm.), $n^{20}D$ 1.3840, and 27 g. of a second fraction, b.p. 95–126°, containing 90% methyl isobutyrate by gas chromatography. Total ester represented 108% of the theoretical amount of methyl isobutyrate, based on evolution of 1 mole per mole of the original keto ester.

A mixture of 110 g. (2 moles) of sodium methoxide and 1 l. of tetrahydrofuran was heated to reflux, and a mixture of 344 g. (2.0 moles) of methyl 2,2,4-trimethyl-3-oxovalerate and 253 g. (2.0 moles) of benzyl chloride was added over a period of 25 min. The reaction mixture was refluxed for 2 hr., allowed to stand overnight, and then refluxed for 5 hr. Acetic acid (20 ml.) was added, the mixture was filtered, and the solid material was washed with tetrahydrofuran. The solvent was stripped from the combined filtrate and washings, and the residue was fractionated in a 1.8 × 51-cm. column packed with protruded packing. Three major fractions were obtained: methyl isobutyrate, 124.5 g. (70%), b.p. 92–92.5° (730 mm.), $n^{20}D$ 1.3832–1.3833; methyl phenylpivalate, 150 g. (45%), b.p. 112–115° (10 mm.), $n^{20}D$ 1.4963; and methyl 2,2,4,4-tetramethyl-3-oxo-5-phenylvalerate, 68 g. (13%), b.p. 115–166° (10 mm.), $n^{20}D$ 1.5017–1.5021.

Methyl isobutyrate was confirmed by comparison of the infrared spectrum with that of authentic material. The methyl phenylpivalate [b.p. 102–103° (10 mm.), $n^{25}D$ 1.4945[12]] was checked by saponification.

Anal. Calcd. for $C_{12}H_{16}O_2$: sapon. equiv., 192.2. Found: 192.4.

The methyl 2,2,4,4-tetramethyl-3-oxo-5-phenylvalerate, after recrystallization from methanol, melted at 38.5–40°; the melting point of a mixture with previously prepared material showed no depression.

Cleavage of Methyl 2,2,4,4-Tetramethyl-3-oxo-5-phenylvalerate with Sodium Methoxide.—A mixture of 20.6 g. (0.08 mole) of methyl 2,2,4,4-tetramethyl-3-oxo-5-phenylvalerate, 4.35 g. (0.08 mole) of sodium methoxide, and 9.85 g. (0.08 mole) of benzyl chloride in 50 ml. of tetrahydrofuran was stirred and heated under reflux for 8 hr. and allowed to stand overnight. Acetic acid (1.0 ml.) was added, and the mixture was filtered. Analysis by gas-liquid chromatography indicated the following solvent-free composition (area percent, uncorrected): methyl phenylpivalate, 74%; methyl 2,2,4,4-tetramethyl-3-oxo-5-phenylvalerate, 17%; benzyl chloride, 8%; unknown, 1%.

Preparation of Diethyl Dimethylmalonate.—Sodium ethoxide was prepared by dissolving 11.5 g. (0.5 g.-atom) of sodium in 125 ml. of absolute ethyl alcohol, evaporating the excess alcohol under reduced pressure, and finally drying the sodium ethoxide at 70° under 1 mm. pressure for 4 hr. Freshly distilled diethyl carbonate (750 ml., b.p. 123.5–124°) was added to the sodium ethoxide and the mixture was stirred while 140 g. (1.0 mole) of tetramethyl-1,3-cyclobutanedione was added. The mixture was stirred for 1 hr., refluxed for 2.5 hr., and allowed to stand for 2 days. It was then poured into ice water, and the organic layer was separated and dried over magnesium sulfate. Distillation at atmospheric pressure removed the lower boiling components; when the base temperature reached 200°, the residue was transferred to a smaller flask and the distillation was continued under reduced pressure through a 25 × 1.8-cm. packed column. The yield of diethyl dimethylmalonate, b.p. 80–81° (10 mm.), $n^{20}D$ 1.4130, was 186 g. (50%). The ester was characterized by saponification in alcoholic potassium hydroxide; the dimethylmalonic acid recovered melted at 190–192°.

Preparation and Cleavage of *tert*-Butyl 2,2,4-Trimethyl-3-oxovalerate.—Tetramethyl-1,3-cyclobutanedione (140 g., 1.0 mole) was added cautiously to a solution of 5 g. of sodium methoxide in 250 ml. of *tert*-butyl alcohol at 60–70°. After addition was complete, the mixture was stirred and heated under a reflux condenser. When the temperature reached 90–100°, an exothermic reaction occurred, and the mixture refluxed vigorously and became gelatinous. Stirring and heating were continued for about 3 hr. The product was then acidified with 10 ml. of acetic acid and distilled to give 196 g. (68%) of *tert*-butyl isobutyrate, b.p. 59–63° (77 mm.), $n^{20}D$ 1.3918.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.6; H, 11.2. Found: C, 66.7; H, 11.3.

***tert*-Butyl 2,2,4-Trimethyl-3-oxovalerate.**—A solution was prepared by addition of 4 g. of a 50% dispersion of sodium hydride in mineral oil to 250 ml. of *tert*-butyl alcohol, and 140 g. (1 mole) of tetramethyl-1,3-cyclobutanedione was added gradually with stirring at 30–40°. The mixture was stirred for about 30 min. and then heated cautiously to 60°. The reaction suddenly became exothermic: The temperature rose rapidly and the mixture became gelatinous and began to reflux. When the reaction subsided, the mixture was stirred for 1 hr., acidified with 10 ml. of acetic acid, and distilled. The yield of *tert*-butyl 2,2,4-trimethyl-3-oxovalerate, b.p. 100–104° (16 mm.), $n^{20}D$ 1.4212, was 156 g. (73%).

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.3; H, 10.3. Found: C, 66.9; H, 10.3.

(12) S. M. McElvain and C. L. Aldridge, *J. Am. Chem. Soc.*, **75**, 3990 (1953).