Ring Cleavage of 2,2,4-Trimethyl-3-hydroxy-3-pentenoic Acid β-Lactone by the Anion of Diisopropyl Ketone[1]

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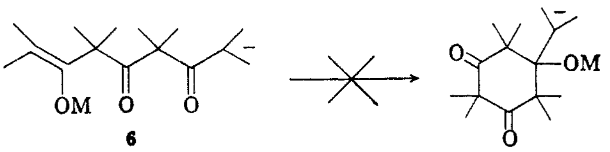
The condensation of phenyl Grignard reagent with excess 2,2,4-trimethyl-3-hydroxy-3-pentenoic acid β-lactone (1) produced a triketone and a hydroxy diketone the structures of which were elucidated by instrumental and chemical methods. Mechanism of the reaction is postulated to involve reaction of anion intermediates of diisopropyl ketone with lactone 1 in a ring-opening process.

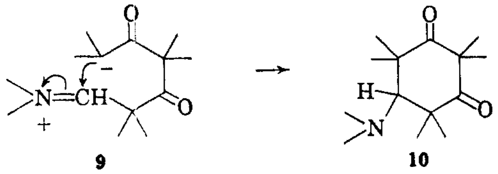
Recent information on reactions involving ring cleavage of β-lactones by Grignard reagents demonstrates clearly that a multitude of products often results.[2a,b] The lactone, 2,2,4-trimethyl-3-hydroxy-3-pentenoic acid β-lactone (1), was reported to condense with aryl Grignard reagents to give highly substituted β-diketones[2c] (Scheme I). Evidence is now available to suggest that a mono enol anion (2) and a dianion (3 or 4) are formed which in the presence of an excess of 1 may react to form a new anion. Hydrolysis of the reaction mixture gives 7 and 8 in relatively low yields.

Insufficient Grignard reagent allows the excess lactone 1 to react with 2, 3, or 4 to give the new anion 5 or 6. Cyclization of the anion 5 can conceivably occur; hydrolysis of the reaction product would lead to 8. The structure 5 may be favored over 6 because ring closure of the latter would give a tertiary carbanion the stability of which may be less than 8a, the precursor of 8. It is not possible to fully disprove the intermediacy of 6, however. The stability of the enols 2 and 6 compared to keto forms 4 and 5 cannot be evaluated from the data at hand. Thus a definitive assignment of whether 5 or 6 is the precursor of 8a is not permitted. Since gas chromatography indicates more than a dozen minor components, the anions 2, 3, 4, 5, or 6 may be involved in other reaction sequences.



6

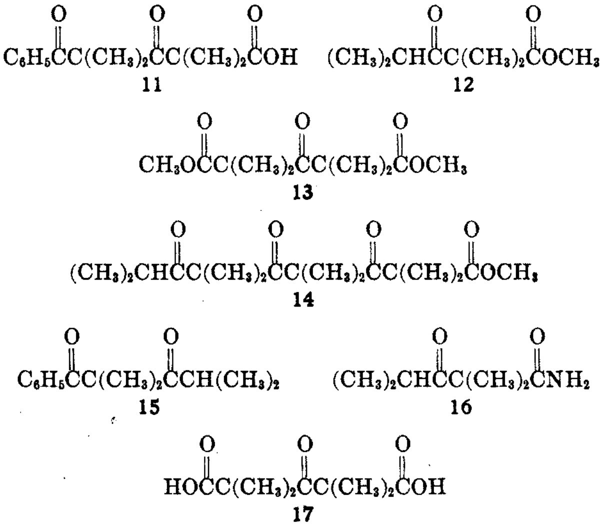
A cyclization similar to that shown for 5 has been observed in the formation of 5-dimethylamino-2,2,4,4,6,6-hexamethyl-1,3-cyclohexanedione[3] (10). The cyclization of the carbanion intermediate 9 in this case involves attack on a carbon atom of an enamine rather than a carbonyl carbon atom.



9 10

In order to demonstrate the intermediacy of anions 2, 3, 4, 5, or 6, the reaction mixture of phenyl Grignard reagent and 1 was carbonated. The acidified, aqueous sodium bicarbonate extract of the resulting organic layer gave 11 (3%) and an oil. Keto acid 11 was identified by nmr (see Table I) and infrared analysis and by its conversion with heating at its melting point into 1-phenyl-2,2,4-trimethyl-1,3-pentanedione (15). (See Chart I.)

CHART I



$C_6H_5\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OH$ 11

$(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3$ 12

$CH_3O\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3$ 13

$(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3$ 14

$C_6H_5\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}CH(CH_3)_2$ 15

$(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}NH_2$ 16

$HO\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OH$ 17

Treatment of the aforementioned oil with diazomethane led to the esters 12 (6%), 13 (1%), and 14 (18%). Also identified with the esters were 7 (16%), 15 (2%), and 16 (2%). The formation of 16 probably originates from attack of ammonium chloride on 1. Yields are based on lactone 1.

The structure of 13 was substantiated by an alternate synthesis involving the reaction of 1 with methyl chloroformate and sodium methoxide in tetrahydrofuran.[4] Ester 12 was prepared by treating 1 with anhydrous hydrogen chloride[4] followed by esterification of the resulting acid chloride with methanol in the presence of triethylamine.[5] Ester 14 was isolated from the reaction mixture by preparative gas chromatography (Scheme II). Infrared analysis of 14 indicated absorption at 1757, 1721, 1699 (carbonyl groups), 1390, 1372, and 1350 cm^{-1} with bands of strong intensity at 1265, 1154, and 983 cm^{-1}. Nmr signals observed in deu-

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(1) We wish to express our thanks to the Research Foundation in the Oklahoma State University for partial support. This work is abstracted in part from the thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Oklahoma State University. One of us (R. B. H.) expresses thanks for a National Science Foundation traineeship for 1966–1967.

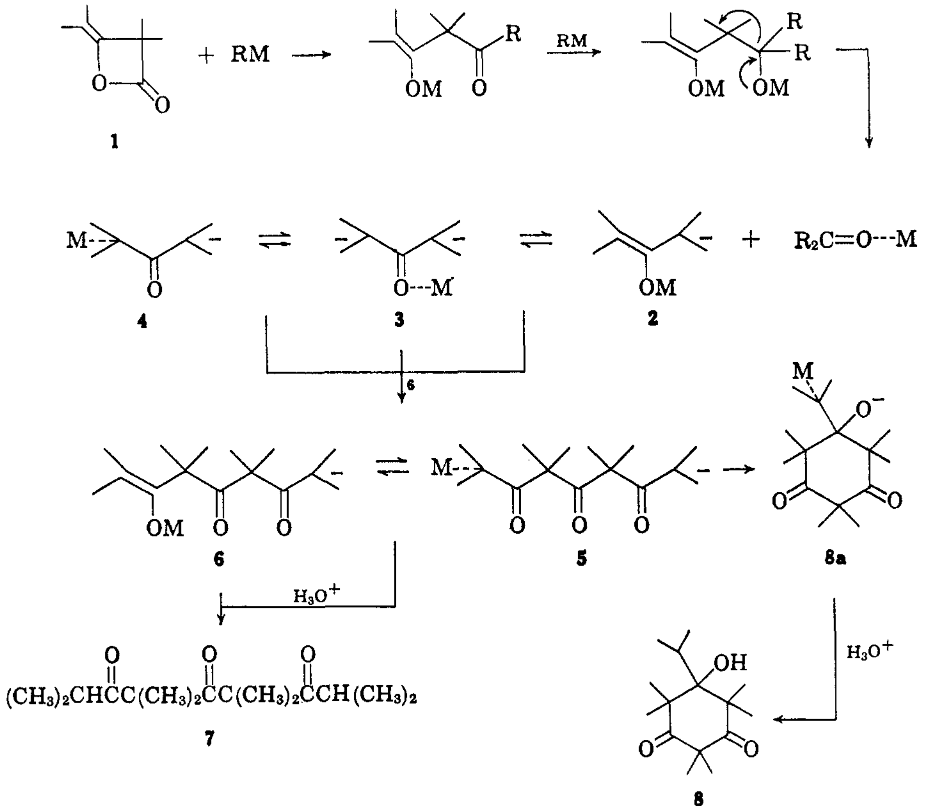
(2) (a) C. G. Stuckwisch and J. V. Bailey, *J. Org. Chem.*, **28**, 2362 (1963); (b) D. V. Nightingale and R. H. Turley, *ibid.*, **26**, 2656 (1961); (c) K. D. Berlin and M. H. Cooper, *ibid.*, **29**, 2057 (1964).

(3) R. H. Hasek and J. C. Martin, *ibid.*, **28**, 1468 (1963).

(4) "Technical Data Report, No. 129," Eastman Chemical Products, Inc., Kingsport, Tenn., 1961.

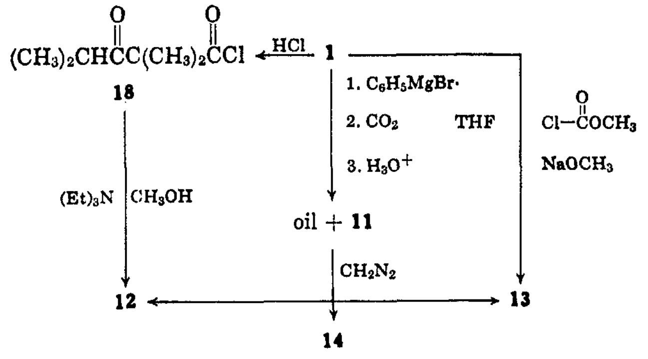
(5) K. D. Berlin, T. H. Austin, and M. Nagabhushanam, *J. Org. Chem.*, **30**, 1267 (1965). A general procedure was followed.

SCHEME I



RM = phenyl, methyl, or ethyl Grignard reagents

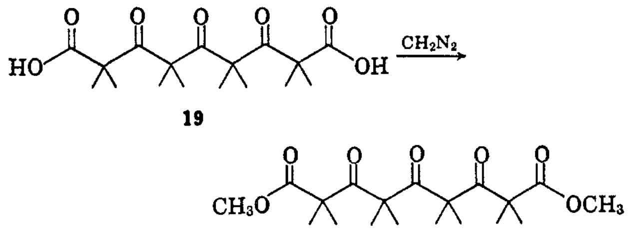
SCHEME II



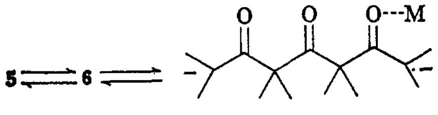
teriochloroform are shown in Table I. Both **15** and **16** were detected by vapor phase chromatography.

The equilibrium postulated among **2**, **3**, and **4** is based upon the fact that the ratio of monoacid (precursor acid of **12**) to diacid **17** remained fairly constant in all runs in ether. This suggests that the anions have a common precursor and that variation in the efficiency of carbonation is minimal. It is not possible to establish whether **3** or **4** is the precursor of the dicarboxylic acid **17** (the acid precursor of **13**), but it is not unreasonable that **2** is carbonated to give the monoacid which reacted with diazomethane to give **12**. When the original condensation was performed in THF, an increase in the ratio of diacid **17** to monoacid was noted. This could possibly be a result of increased solvation of all species present in the reaction mixture or a shift in the equilibrium between **2** and **3**.

Another diacid (**19**) was also present in a small amount (<2%) in the THF reaction mixture and precipitated with diacid **17**. Diacid **19** was difficult to extract from the mixture of acids, but a small amount of the pure diacid was obtained by repeated recrystallization from benzene. Its structure was substantiated by elemental analysis and infrared and nmr spectral data (Table I). Alternatively, part of the mixture of acids was converted to their corresponding diesters **13** and **20** by reaction with diazomethane. Ester **20** which precipitated from the reaction mixture was identified by elemental analysis and infrared and nmr data (Table I). This suggests that **5** or **6** may be in equilibrium with the corresponding dianion **6a**. It is interesting to note in passing that novel diester **20** contains five carbonyl functional groups each of which is β to the other but none of which is enolizable.



19 **20**



6a

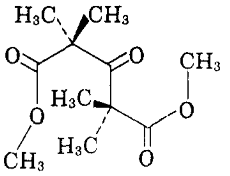
The nmr spectra of both diesters are quite unusual as different chemical shifts are observed for the internal *gem*-dimethyl groups and the ester methyl groups. Conformational representations (shown below) in which the *gem*-dimethyl and ketone groups are shown

TABLE I[a]

Compd	Infrared, cm^{-1} Hydroxyl	Carbonyl	Isopropyl	Nmr chemical shift (δ), ppm
7	. . .	1700 (sh at 1722)	1390, 1370	3.08 (m) (J = 7 cps), 1.34 (s), 1.04 (d) (J = 6.5 cps)
8	3460	1692 (sh at 1718)	1390, 1378	1.90 (s), 1.43 (d) (J = 7 cps), 1.19 (d) (J = 6 cps), 0.91 (d) (J = 6.5 cps)
11	3210	1708 (sh at 1730)	. . .	9.05 (s), 7.80 (s) (br), 7.25 (m) (br), 1.65 (s), 1.38 (s)
12	. . .	1725 (sh at 1742)	. . .	3.72 (s), 2.91 (m) (J = 6.5 cps), 1.32 (s), 1.04 (d) (J = 7 cps)
13	. . .	1775 (sh at 1723)	. . .	3.79 (s), 3.68 (s), 1.53 (s), 1.30 (s)
14	. . .	1757, 1721, 1699	1390, 1372	3.75 (s), 3.13 (m) (J = 7 cps), 1.44 (s), 1.38 (s), 1.04 (d) (J = 7 cps)
18	. . .	1788, 1725	1390, 1373	3.04 (m) (J = 7 cps), 1.54 (s), 1.15 (d) (J = 7 cps)
19	. . .	2730 (br) 1756, 1700	. . .	11.68 (s), 1.57 (s) (sh at 1.54), 1.45 (s) (sh at 1.39)
20	. . .	1755, 1730, 1699	1395, 1380	3.79 (s), 3.70 (s), 1.55 (s), 1.53 (s), 1.45 (s), 1.34 (s)
22	3510	1690 (sh at 1720)	. . .	2.47 (s), 1.40 (d) (J = 7 cps), 1.16 (s), 0.93 (s)
24	. . .	1718 (sh at 1737)	1390, 1370	4.26 (q) (J = 7 cps), 2.81 (m) (J = 7 cps), 1.34 (s), 1.30 (t) (J = 7 cps), 1.07 (d) (J = 6.5 cps)
26	. . .	1703 (sh at 1721)	1390, 1377	2.88 (m) (J = 7 cps), 1.33 (s), 1.03 (d) (J = 6.5 cps)

[a] s (singlet), d (doublet), m (multiplet), q (quartet), t (triplet). Solvents for nmr spectra: compounds **7, 13, 24, 26** (CCl_4); **8, 22** (benzene); **12, 18** (neat); **11** (pyridine-d_5); **14, 20** ($CDCl_3$). Compound **11** decomposes rapidly to **15** on standing in pyridine.

in the *anti* or staggered conformation point out that different environments for the methyl groups can be envisioned. In benzene above 50° the δ values changed for each of the signals suggesting a possible conformation change.



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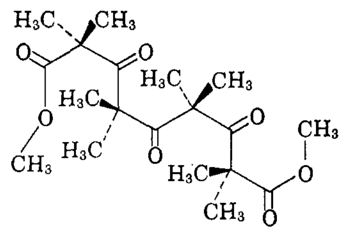
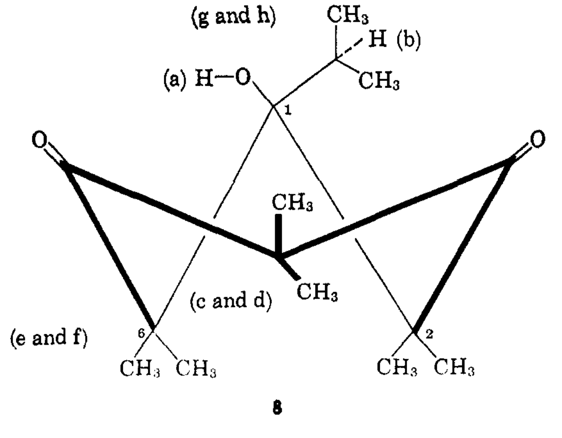


20

When phenyl Grignard reagent and **1** were allowed to react in a ratio of 1:1.2, respectively, **8** was obtained in a maximum yield of 30% and could be recrystallized directly from the reaction mixture. In the perspective drawing the dark lines are bonds directed out in front of the plane on the paper. The thin lines representing bonds C-1–C-2 and C-1–C-6 are in the plane of the paper. Substituents at C-1, C-2, and C-6 are not represented in a specified plane. Elemental analysis indicated an empirical formula of $C_{15}H_{26}O_3$ with a molecular weight of 253. Infrared absorptions occurred at 3460 (hydroxyl group), 1692 (carbonyl group, shoulder at 1718), 1390, and 1378 cm^{-1} (isopropyl group). The nmr spectrum displayed signals in benzene at δ 1.90 (singlet), 1.43 (doublet, J = 7 cps), 1.19 (doublet, J = 6 cps), and 0.91 (doublet, J = 6.5 cps) in the ration 1:6:12:6, respectively (see **8** below for proton assignments). The tertiary proton in **8** was not immediately visible, but at high-spectrum amplitude shoulders were observed near the methyl proton resonances c and d suggesting that much of the expected heptet for proton b was obscured under the methyl protons. The question was resolved when the nmr spectrum was determined in pyridine. Enhanced chemical shifts placed the heptet of proton b at δ 2.38 clearly outside the area of the methyl resonances.



8

High-resolution nmr (100 Mc) in benzene revealed five of the seven peaks for the expected heptet for proton b on **8**. The doublet at δ 1.43 has been assigned to protons c and d, while the doublet at 1.19 is due to the methyl protons e and f and the doublet at 0.91 to the methyl protons of the isopropyl groups (g and h). Decoupling protons g and h from the tertiary proton b (downfield, 273.3 cps) resulted in the collapse of the doublet due to protons g and h showing that these protons are the methyl protons on a true isopropyl group. Splitting of the *gem*-dimethyl resonances may result from a preferred conformation imposed upon the system by steric requirement of the isopropyl group and geometric stipulations by the 1,3-dicarbonyl system. Because of the lack of a model similar to **8**, assignment of the methyl resonances c and d and e and f to individual methyl groups could not be determined. This situation is contrasted with the nmr spectrum of **7** which displays two sets of equivalent, internal *gem*-dimethyl groups as one signal, although this is predictable on the basis of internal free rotation of the alkyl groups. The nmr spectrum of hexamethyl-1,3,5-cyclohexanetrione (in benzene) contains a single absorption for the methyl protons. Dipole moment studies indicate that this triketone probably exists in a twisted, flexible boat conformation.[6] This form shows an equivalency of all methyl groups.

Dreiding models imply that a chair conformation for **8** is rigid and has imposing 1,3 interactions of axial methyl groups. A twisted chair form can be constructed, however, in which interactions of nonbonded groups are minimized as shown in the structural representation of **8**.

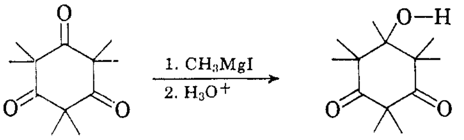
Methyl and ethyl Grignard reagents condensed with **1** to give compounds **7** and **8**. The yield of **7** was higher than **8** in both cases and many other products formed in low yields were detectable by glpc.

[6] J. Dale, *J. Chem. Soc.*, 1028 (1963).

In an attempt to prepare **8**, hexamethyl-1,3,5-cyclohexanetrione (**21**) was treated with isopropyllithium or isopropyl Grignard reagent (in the presence of magnesium bromide).[7] Glpc analysis of the reaction mixture in either case showed that **7** was produced (<10%) and other products resulting from reduction of carbonyl groups. Starting material (50–55%) was also recovered.

The hydroxy diketone **8** was inert to bromine in carbon tetrachloride and potassium permanganate, facts suggesting the absence of a double bond. Attempted dehydration of **8** with potassium hydrogen sulfate at 155° for 1 hr resulted in a 62% conversion to **7** as was the case when hydrochloric acid was the catalyst. Treatment of **8** with dimethyl sulfoxide at 178° for 9 hr resulted in a 98% conversion to **7**.

In an effort to prepare a model similar to that of **8**, hexamethyl-1,3,5-cyclohexanetrione (**21**) was allowed to condense with methyl Grignard reagent. A solid product (**22**) obtained had an infrared spectrum which bears a striking resemblance to that of **8** (see Table I).



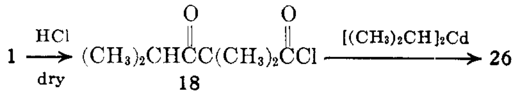
21 **22**

Infrared bands for the monoaddition product **22** were observed at 3420 (hydroxyl group) and 1690 cm^{-1} (carbonyl group, shoulder at 1720 cm^{-1}). The nmr spectrum revealed signals in benzene at δ 2.47 (singlet), 1.40 (doublet, J = 7 cps), 1.16 (singlet), and 0.93 (singlet) in the ratio 1:3:12:6. Elemental analysis indicated the expected empirical formula $C_{13}H_{22}O_3$.

The 1:1 reaction of **8** with potassium hydroxide in absolute ethanol gave **7**, ethyl isobutyrate (**23**), ethyl 2,2,4-trimethyl-3-oxovalerate (**24**), diisopropyl ketone (**25**), potassium carbonate, and 2,4,4,6-tetramethyl-3,5-heptanedione (**26**). Since **7** was present in the reaction mixture the mechanism of the reaction is postulated as shown in Scheme III.

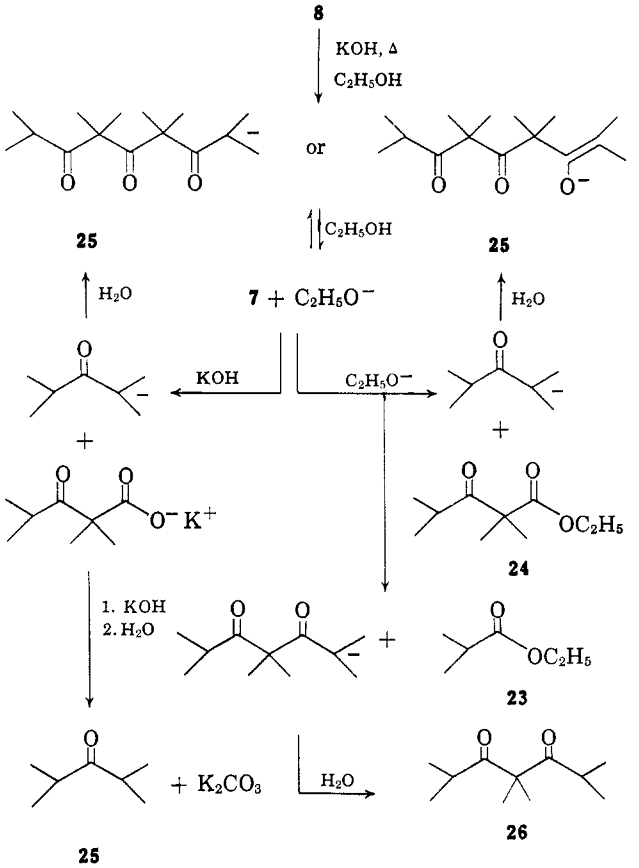
Although attack by base at the carbonyl carbon atom in **8** could occur, no simple mechanism could be written which would involve the formation of **7**. Since basic hydrolysis of **7** gave identical products as found from **8**, the former is a reasonable product in the initial cleavage of **8**. Moreover, no other fragments were detected which were conceivable from attack of hydroxide ion on the carbonyl group of **8**. Consumption of base is not sufficient to cleave all acyl carbon bonds and ethoxide ion is postulated to form and become a competitive base.

Compounds **23** and **25** were identified by gas chromatography and isolation of **24** and **26** was achieved with preparative gas chromatography. Structures of both **24** and **26** were substantiated by nmr and infrared analyses. Additional proof of structure **26** was obtained when it was synthesized by an alternative route involving a cadmium reagent.

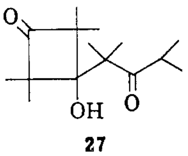


$$1 \xrightarrow[\text{dry}]{\text{HCl}} \underset{\textbf{18}}{(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}Cl} \xrightarrow{[(CH_3)_2CH]_2Cd} 26$$

SCHEME III



Although **7** and **8** possess carbonyl groups, normal procedures[8] failed for the preparation of an oxime, 2,4-dinitrophenylhydrazone, or semicarbazone derivative. In contrast, a structure such as **27**, which could be envisioned as an alternate structure for **8**, might be expected to form normal carbonyl derivatives as does **28**.[9] Attempted esterification of **8** with acetic anhydride in pyridine[10] was also unsuccessful. As was noted previously, treatment of **8** with acid or base resulted in carbon–carbon bond scission although **7** is stable in either hydrochloric or sulfuric acids.



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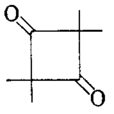

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Other evidence in favor of the six-membered diketone **8** is afforded by infrared data. A band at 1779 cm^{-1} was recorded for the carbonyl groups[3] in **29**, while **28** exhibits a doublet at 1745 and 1721 and **21** has a broad band at 1698 cm^{-1}. For comparison, **8** has a peak at 1694 with a sharp band of lower intensity at 1718 cm^{-1}. Most convincing was the similarity of the carbonyl absorptions of **8** to those of **30** as twin carbonyl peaks were reported for the latter at 1718 and 1688

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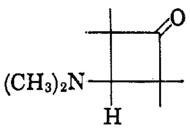
[7] C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, **73**, 870 (1951).

[8] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1964.

[9] E. Wedekind and W. Weisswange, *Ber.*, **39**, 1631 (1906).

[10] G. Buchi, M. Scharch, V. Witterau, and D. M. White, *J. Am. Chem. Soc.*, **81**, 1968 (1959).



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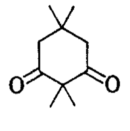
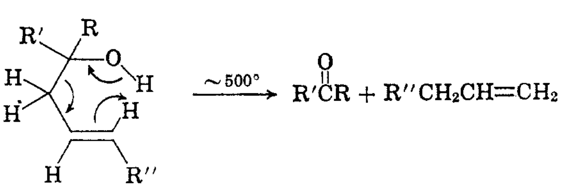


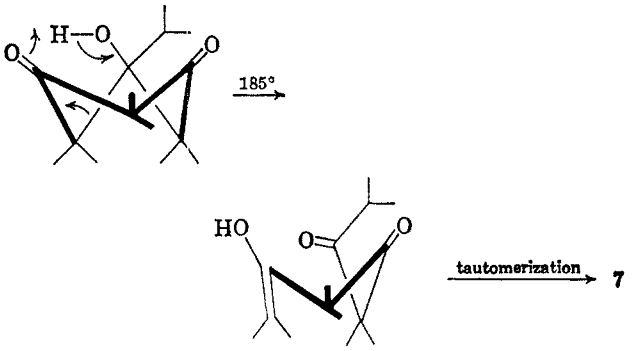
30

cm^{-1} in chloroform.[11] The spectrum of **8** in potassium bromide or chloroform contained the two bands mentioned previously for the carbonyl groups in positions nearly identical with those in **30**.

Triketone **7** was initially isolated by preparative gas chromatography from the reaction of **8** with potassium hydrogen sulfate. It was found that thermal heating of **8** at 185° for 1 hr gave **7** in quantitative yield. Although pyrolysis of this type is rare in the literature, an analogy may be found in the pyrolysis of β-hydroxy olefins the mechanism of which is believed to involve a cyclic transition state.[12]



Models imply that nonbonded interactions are minimal in the twist conformation for **8** but the hydroxyl proton can rotate close to an oxygen atom of a β-carbonyl function. One rationale for the apparent lower activation energy for thermal conversion of **8** to **7** compared to the analogous pyrolysis of β-hydroxy olefins is perhaps found in the conformational rigidity of the ring in **8** which may increase the internal strain.



Elemental analysis of **7** indicates an empirical formula of $C_{15}H_{26}O_3$; a molecular weight of 254 was found to be identical with that for **8**. Infrared absorptions were visible at 1700 (carbonyl group, shoulder at 1722), 1390, 1370, and 1348 (isopropyl group), with intense bands at 1018 and 988 cm^{-1}. The nmr spectrum displayed signals in carbon tetrachloride at δ 3.08 (multiplet, J = 7 cps), 1.34 (singlet), and 1.05 (doublet, J = 6.5 cps).

Slow evolution of HBr was noted when **7** was treated with bromine in carbon tetrachloride which indicates an active hydrogen. Compound **7** was inert to potassium permanganate. When **7** was boiled in a 3-mole excess of 2,4-dinitrophenylhydrazine reagent for 17 hr, recovery of starting material was quantitative. This is unusual since diisopropyl ketone gives a derivative although the reaction is slow.[13]

A 1:1 molar reaction of **7** with ethanolic potassium hydroxide gave products identical with those found from the same reaction with **8** except that **7** was totally consumed in the former case. A mechanism for formation of products from **7** is representative of a classical attack on the carbonyl carbon atom which is known to occur in 1,3-diketone systems.[14]

Experimental Section

Materials.—Lactone **1** was obtained from Eastman Chemical Products, Inc., Kingsport, Tenn., and was freshly distilled [bp 170° (732 mm)] before being used. Melting points are corrected, boiling points are uncorrected. Elemental analyses and molecular weight determinations were performed by the Galbraith Laboratories, Inc., Knoxville, Tenn., or by the Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were obtained on a Beckman IR-5A. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 spectrometer using tetramethylsilane (TMS) as an internal reference. The 100-Mc nmr analysis of compound **8** was performed at Monsanto Chemical Co.; the molecular weight determination of **7** and **8** was done on a Microlab vapor pressure osmometer. Glpc analyses were performed on an Aerograph Model A-550 and a Varian-Aerograph Model 1520 (Hy-Fi) hydrogen flame detection unit and a Model A-700 Autoprep unit. The columns used on the Autoprep unit was a 10 ft × $^3/_8$ in. and a 20 ft × $^3/_8$ in., packed with 15% DEGS on acid-washed Chromosorb W and 30% DEGS on acid-washed Chromosorb W, respectively. We wish to express our thanks to Mrs. Margaret H. Cooper for a few preliminary experiments.

Reaction of Phenyl Grignard Reagent with Lactone 1.—Phenylmagnesium bromide was prepared from 24.00 g (1.0 g-atom) of magnesium and 157.02 g (1.0 mole) of bromobenzene in 800 ml of anhydrous ethyl ether. To the chilled (0°) Grignard reagent was added dropwise (with stirring under N_2) a solution of **1** (168.12 g, 1.2 moles) in 150 ml of anhydrous ether at such a rate to maintain the temperature below 15°. The resulting orange mixture was stirred overnight at room temperature and then heated under reflux for 6 hr. The mixture was hydrolyzed at room temperature with cold 20% aqueous ammonium chloride and the two-layer mixture was extracted with ether. The ether extracts were dried ($MgSO_4$) and filtered and the ether was removed giving 100 ml (approximately) of a yellow oil. An equal volume of Skellysolve F was added and the solution was chilled with the formation of a white solid. Filtration and recrystallization from benzene–heptane afforded 42.10 g (27%) of **8** as clear platelets, mp 148–149°; the molecular weight was 253 (benzene).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.86; H, 10.23. Found: C, 71.18; H, 10.32.

Analysis of the filtrate by glpc (hydrogen flame unit, column 6 ft × $^1/_8$ in., packed with 6% Silicone-30, DMCS treated on Chromosorb G, temperature 152°) showed the presence of **7** (9%) with benzophenone and diisopropyl ketone as major components.

Carbonation of the Mixture from Reaction of Phenyl Grignard Reagent and Lactone 1.—Phenylmagnesium bromide (1.0 mole) in 800 ml of anhydrous ethyl ether was chilled to 4° and **1** (168.12 g, 1.2 moles) in 175 ml of anhydrous ether was added dropwise (with stirring under N_2) to maintain the temperature below 15°. The orange mixture was heated under reflux for 6 hr, allowed to cool to room temperature, and then treated with carbon dioxide gas (bubbled through the mixture with stirring) for 28 hr. Hydrolysis of the mixture at room temperature was effected with cold 20% aqueous ammonium chloride, and the aqueous phase was extracted with ether. The organic layer was extracted with 1 l. of 10% aqueous sodium bicarbonate, and the aqueous layer was acidified with 6 *N* HCl to a pH of 1. The ether extracts were dried ($MgSO_4$) and filtered, and the solution was concentrated; 8.36 g (3%) of **11** precipitated, mp 147.5–149° (after recrystallization from acetone); when the residual ether was removed, an oil remained.

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[11] B. Eistert and W. Reiss, *Chem. Ber.*, **87**, 92 (1954).

[12] R. T. Arnold and G. Smolinsky, *J. Am. Chem. Soc.*, **82**, 4918 (1960).

[13] H. L. Herzog and E. R. Buchman, *J. Org. Chem.*, **16**, 99 (1951).

[14] H. H. Wasserman, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 7.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87. Found: C, 68.61; H, 6.80.

A 1-g (0.004 mole) sample of **11** was heated slowly to 150° and held there for 1 hr. When cool, the contents (liquid) were analyzed by glpc; **15**[15] was the only component detected in quantitative yield based on **11**.

The aforementioned oil (25.01 g) was treated with 12 g (0.29 mole) of diazomethane. The resulting golden oil was analyzed by glpc (hydrogen flame detection unit, column 6 ft × 0.25 in., packed with 10% Silicone-30, DMCS treated on Chromosorb G, temperature 167°) and showed the presence of **7** (19%), **12** (6%), **13** (1%), **14** (18%), **15** (2%), and **16** (2%).[16]

Preparative gas chromatography (20-ft column autoprep unit, 195°) gave pure **14** (19%), n^{23}D 1.4641. Glpc analysis on the hydrogen flame unit (same column as cited above) indicated only one component.

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.38; H, 8.97. Found: C, 65.17; H, 8.77.

Carbonation of the Mixture from Reaction of Phenyl Grignard Reagent and Lactone 1 in THF.—Phenylmagnesium bromide (1.0 mole) in 800 ml of anhydrous ether was chilled to 4°, and **1** (168.12 g, 1.2 moles) in 200 ml of anhydrous ether was added dropwise with stirring to maintain the temperature below 15°. The ether was removed by distillation, and THF was added until the temperature of the dark red solution reached 68°. The solution was heated at this temperature for 7 hr and cooled to 30°; carbon dioxide was bubbled through the solution for 24 hr with stirring. The mixture was hydrolyzed at room temperature with cold 20% aqueous ammonium chloride, and the aqueous phase was extracted with ether. The organic layer was extracted with 1.5 l. of 10% aqueous sodium bicarbonate, and the aqueous layer was acidified with 6 *N* HCl to pH 1. The ether extracts were dried ($MgSO_4$) and filtered, and the ether was removed to give 8.24 g of a white solid, mp 134–135° dec,[17] and an oil (39.34 g). Pure **19** was exceedingly difficult to extract from the solid. Repeated recrystallizations from benzene gave a small amount (<100 mg) of the pure diacid **19**, mp 121–122°.

Anal. Calcd for $C_{17}H_{26}O_7$: C, 59.64; H, 7.60. Found: C, 59.35; H, 7.20.

Part of the mixture of diacids was treated with excess diazomethane. Diester **20** (2.5% based on **1**) precipitated and was recrystallized from Skellysolve F (mp 74–75°). Nmr and infrared data for **20** are given in Table I.

Anal. Calcd for $C_{19}H_{30}O_7$: C, 61.60; H, 8.10. Found: C, 61.64; H, 8.13.

The aforementioned oil was treated with 18 g (0.43 mole) of diazomethane. The amber oil was analyzed by glpc (hydrogen flame detection unit, column 6 ft × $^1/_8$ in., packed with 6% Silicone-30, DMCS treated on Chromosorb G, temperature 152°) and revealed the presence of **7** (13%), **12** (4%), **13** (8%), **14** (12%), **15** (3%), and **16** (2%).

Dimethyl 2,2,4,4-Tetramethyl-3-pentanedioc Acid (13).—To a stirred suspension of sodium methoxide (18.60 g, 0.34 mole) heated at reflux in 190 ml of THF was added **1** (46.65 g, 0.34 mole). The mixture was heated 10 min after the addition. The mixture was chilled and added to a stirred solution of methyl chloroformate (31.50 g, 0.33 mole) in 90 ml of tetrahydrofuran over a period of 0.5 hr. Intermittent cooling was used to keep the temperature below 50°. After the addition, the mixture was heated under reflux for 0.5 hr, acidified with acetic acid, and filtered, and the solvent was removed by distillation to give 51.01 g of a light yellow liquid. Vacuum distillation through a 54-cm Vigreux column gave 47.00 g (62%) of **13** as a clear liquid, bp 110–112° (6 mm), n^{21}D 1.4481 [lit.[4] bp 97–98° (3 mm), n^{20}D 1.4470–1.4480].

2,2,4-Trimethyl-3-oxovaleryl Chloride (18).—Hydrogen chloride gas was bubbled through **1** (140.1 g, 10 moles) for 40 hr. The reddish brown solution was distilled through an 18-in. glass helices column giving 93.19 g (53%) of **18**, bp 181–183° (729 mm), n^{28}D 1.4362 [lit.[4] bp 85–86° (23 mm), n^{20}D 1.4410].

Methyl 2,2,4-Trimethyl-3-oxovalerate (12).—Triethylamine (37.44 g, 0.37 mole) in 150 ml of anhydrous ether was added over a period of 1 hr to **18** (59.78 g, 0.37 mole) in 200 ml of anhydrous ether. Methanol (18.24 g, 0.57 mole) in 150 ml of anhydrous ether was added over a period of 1.25 hr. The mixture was heated at reflux for 1.5 hr, chilled, and filtered. Removal of ether gave 52 ml of a light yellow liquid. Distillation through an 18-in. tantalum wire column gave 44.00 g (76%) of **12**, bp 188–189.5° (729 mm), n^{20}D 1.4215 [lit.[18] bp 88–91° (22 mm), n^{20}D 1.4244].

Reaction of Methylmagnesium Iodide with Lactone 1.—The Grignard reagent (0.5 mole) in 500 ml of anhydrous ether was added dropwise with stirring to maintain the temperature below 15°. The cloudy, orange solution was heated under reflux for 12 hr and then hydrolyzed at room temperature with cold 20% aqueous ammonium chloride. The work-up (same as that used in the reaction of phenyl Grignard reagent and **1**) gave 50 ml (approximately) of a yellow oil. No precipitate formed on cooling. Glpc analysis (hydrogen flame detection unit, column 6 ft × $^1/_8$ in., packed with 4% Silicone-30, DMCS treated on Chromosorb G, temperature 167°) showed the presence of **7** (76%) along with more than a dozen other components.

Reaction of Ethyl Grignard Reagent and Lactone 1.—The Grignard reagent (0.15 mole) in 370 ml of anhydrous ether was chilled to 0° and **1** (70.0 g, 0.5 mole) in 75 ml of anhydrous ether was added dropwise with stirring to keep the temperature below 15°. (The procedure and work-up are the same as the reaction between phenyl Grignard reagent and **1**). Work-up gave an oil which when chilled gave a white solid. Recrystallization from benzene–heptane afforded 123 mg of **8**. Glpc analysis of the filtrate (hydrogen flame detection unit, column 6 ft × $^1/_8$ in., packed with 4% Silicone-30, DMCS treated on Chromosorb G, temperature 167°) showed the presence of **7** (60%) along with many other minor components.

Attempted Reaction of Hexamethyl-1,3,5-cyclohexanetrione (21) and Isopropyllithium.—Isopropyllithium reagent, prepared from 9.8 g (0.125 mole) of isopropyl chloride and 2 g (0.29 mole) of lithium dust[19] in Skellysolve F (yield, 72%), was added to a stirred solution of **21** (20.00 g, 0.09 mole) in 100 ml of dry Skellysolve F at −30°. After stirring at room temperature for 12 hr the grey mixture was hydrolyzed by adding dropwise 175 ml of water. Extraction of the aqueous layer with ether–Skellysolve F (50:50) gave organic extracts which were combined with the original organic layer. The combined organic solution was dried ($MgSO_4$), and the solvent was evaporated to give 18.88 g of a yellow liquid. When the liquid was chilled, a white solid crystallized but could not be further purified. Glpc analysis (hydrogen flame detection unit, column 6 ft × $^1/_8$ in., packed with 5% Silicone-30, DMCS treated on Chromosorb G, temperature 162°) showed starting material (53%), **7** (8%), and several other products.

Reaction of Hexamethyl-1,3,5-cyclohexanetrione (21) with Isopropylmagnesium Bromide in the Presence of Magnesium Bromide.—Bromine (16.0 g, 0.10 mole) was added slowly with stirring to 2.40 g (0.10 g-atom) of magnesium in 85 ml of anhydrous ether. The ketone (20.00 g, 0.10 mole) in 90 ml of anhydrous ether was added to the magnesium bromide solution over a period of 1 hr. To this brown mixture (two layers) was added isopropylmagnesium bromide (yield 78%, 0.08 mole) prepared from 12.30 g (0.10 mole) of isopropyl bromide and 2.40 g (0.10 g-atom) of magnesium in 140 ml of anhydrous ether. After the mixture was stirred overnight at room temperature, the reaction mixture was heated under reflux for 12 hr, chilled, and then hydrolyzed at room temperature by the dropwise addition of cold 20% aqueous ammonium chloride. The ether extracts were dried ($MgSO_4$) and filtered, and the ether was removed to give 19.86 g of a yellow liquid. Glpc analysis (hydrogen flame detection unit, column 6 ft × $^1/_8$ in., packed with 5% Silicone-30, DMCS treated on Chromosorb G, temperature 165°) of the reaction mixture revealed the presence of starting material (92%), **7** (3%), and several minor products.

Attempted Dehydration of Ketol 8.—Ketol **8** (20.00 g, 0.078 mole) was intimately mixed with potassium hydrogen sulfate (20.00 g, 0.147 mole) and heated at 155° for 1 hr. At room temperature, 125 ml of water was added to the reaction mixture and the resulting brown mixture was extracted with ether. The ether extracts were washed with water (200 ml), dried ($MgSO_4$), and filtered, and the ether was distilled to give 19.96 g of a brown oil. Glpc analysis (hydrogen flame detection unit,

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[15] The diketone **15** was previously characterized; see ref 2c.

[16] The keto amide **16** was identical in all respects (infrared and nmr spectrum and melting point with that described by R. H. Hasek, E. U. Elam, and J. C. Martin, *J. Org. Chem.*, **26**, 4340 (1961).

[17] B. Murin, W. Riedl, K. H. Risse, and M. Scheublein, *Ber.*, **92**, 2033 (1959). These authors reported a melting point of 133–134° for **17** which analyzed well.

[18] R. H. Hasek, E. V. Elam, J. C. Martin, and R. G. Nations, *J. Org. Chem.*, **26**, 700 (1961).

[19] P. D. Bartlett, C. G. Swain, and R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 3230 (1941).

column 6 ft × $^{1}/_{8}$ in., packed with 5% Silicone-30, DMCS treated on Chromosorb G, temperature 165°) of the oil showed the presence of **7** (62%). Preparative gas chromatography (autoprep unit, temperature 185°) gave an analytical sample of **7**, mp 19–20°.

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.86; H, 10.23. Found: C, 70.94; H. 10.24.

Attempted Dehydration of Ketol 8 with Dimethyl Sulfoxide.[20]—Dimethyl sulfoxide (30.03 g, 0.385 mole) and 13.90 g (0.055 mole) of **8** were heated in an oil bath at 178° for 11 hr. At room temperature 150 ml of water was added to the mixture and the resulting brown solution was extracted with ether–benzene (50:50). The organic extracts were dried ($MgSO_4$) and filtered, and the solvent was removed giving 13.79 g of a yellow oil. Glpc analysis (hydrogen flame detection unit, column 6 ft × $^{1}/_{8}$ in., packed with 5% Silicone-30, DMCS treated on Chromosorb G, temperature 160°) revealed the presence of **7** in near-quantitative yield (98%).

Attempted Reaction of Hexamethyl-1,3,5-cyclohexanetrione (21) with Methylmagnesium Iodide.—The ketone **21** (20.00 g, 0.10 mole) in 125 ml of anhydrous ether was cooled to 0° and the methyl Grignard reagent (0.10 mole) in 125 ml of anhydrous ether was added dropwise with stirring to keep the temperature below 15°. Hydrolysis was effected by the addition of cold 20% aqueous ammonium chloride. The ether extracts were dried ($MgSO_4$) and filtered and the ether was removed; yield of residual oil was 19.91 g. The oil afforded a white solid when chilled. Recrystallization of the solid from benzene–heptane gave **22** (69%), mp 97.5–98.5°.

Anal. Calcd for $C_{13}H_{23}O_3$: C, 69.03; H, 9.73. Found: C, 68.64; H, 9.60.

Reaction of Ketol 8 with Potassium Hydroxide in Ethanol.—Potassium hydroxide (4.50 g, 0.084 mole) in 200 ml of absolute ethanol was added over a period of 1.5 hr to a stirred solution of **8** (21.50 g, 0.084 mole) in 125 ml of absolute ethanol heated at reflux. When the addition was complete, the solution was heated under reflux for 1 additional hr, chilled, and filtered giving 3.61 g of potassium carbonate. Water (225 ml) was added to the filtrate and the aqueous solution was extracted with ether–benzene (50:50). The organic extracts were dried ($MgSO_4$) and filtered and the solvent was distilled leaving about 104 ml of solution. Glpc analysis (hydrogen flame detection unit, column 6 ft × $^{1}/_{8}$ in., packed with 5% Silicone-30, DMCS treated on Chromosorb G, temperature 160°) revealed the presence of **7**, ethyl isobutyrate (**23**), ethyl 2,2,4-trimethyl-3-oxovalerate (**24**), diisopropyl ketone (**25**), and 2,4,4,6-tetramethylheptane-3,5-dione (**26**). Preparative gas chromatography (autoprep unit, temperature 152°, helium flow 193 cc/min) gave pure samples of **24** and **26**, respectively, n^{20}_{D} 1.4227 (lit.[21] n^{20}_{D} 1.4230) for **24** and n^{20}_{D} 1.4256 (lit.[22] n^{20}_{D} 1.4252) for **26**. Glpc analysis on the hydrogen flame unit indicated only one peak for each sample. Nmr and infrared data (Table I) support these known structures.

Neutralization of the aqueous layer with 6 *N* HCl was followed by extraction with ether. The ether extracts were dried ($MgSO_4$) and filtered, and ether was removed by distillation until 15 ml of solution remained. Glpc analysis (hydrogen flame detection unit, column 6 ft × $^{1}/_{8}$ in., packed with 5% Silicone-30, DMCS treated on Chromosorb G, temperature 89°) revealed only isobutyric acid.

2,4,4,6-Tetramethylheptane-3,5-dione (26).—Isopropylmagnesium bromide was prepared from 12.15 g (0.5 g-atom) of magnesium in 175 ml of anhydrous ether and 61.50 g (0.50 mole) of isopropyl bromide in 200 ml of anhydrous ether (yield 87%). The Grignard reagent was chilled to −10° and dry cadmium chloride (49.00 g, 0.267 mole) was added in 3-g portions over a period of 0.5 hr at room temperature. The solution was then heated under reflux for 1 hr. Ether was removed by distillation and 350 ml of anhydrous benzene was added. The viscous, brown mixture was chilled to −7°, 83.25 g (0.5 mole) of 2,2,4-trimethyl-3-oxovaleryl chloride (**18**) was added, and the resulting mixture was heated under reflux for 3.5 hr. The mixture was chilled to −10° and was hydrolyzed with cold 20% aqueous ammonium chloride. The benzene extracts were dried ($MgSO_4$) and filtered, and the benzene was distilled affording 82.96 g of a brown liquid.

Glpc analysis (hydrogen flame detection unit, column 6 ft × $^{1}/_{8}$ in., packed with 10% silicone rubber on acid-washed Chromosorb W, temperature 66°) showed the presence of **26** (29%), starting material (43%) and several minor components. Preparative gas chromatography (Autoprep unit, 10 ft × $^{3}/_{8}$ in. column, temperature 145°) gave pure **26** (analyzed on hydrogen flame unit; only one component present) identical with that previously found.

Attempted Esterification of Ketol 8.—Ketol **8**, in pyridine and acetic anhydride, was heated under reflux for 15 hr. Normal work-up afforded a white solid (86%), identified as starting material **8**.

Thermolysis of Ketol 8.—Ketol **8** (5.0 g, 0.02 mole) was heated at 185° for 1 hr. Glpc analysis (hydrogen flame detection unit, column 6 ft × $^{1}/_{8}$ in., packed with 5% Silicone-30, DMCS treated on Chromosorb G, temperature 165°) revealed the presence of only **7**.

Reaction of Triketone 7 with Potassium Hydroxide in Ethanol.—Potassium hydroxide (0.672 g, 0.012 mole) in 40 ml of absolute ethanol was added dropwise to a solution of **7** (3.00 g, 0.12 mole) in 20 ml of absolute ethanol heated under reflux. The solution was heated for 1 additional hr. By chilling and filtering the solution, 1.12 g of potassium carbonate was deposited and collected. Water (50 ml) was added to the filtrate and the aqueous solution was extracted with ether. The ether extracts were dried ($MgSO_4$), filtered, and distilled until 22.5 ml (approximately) of solution remained. Glpc analysis of this solution (hydrogen flame detection unit, column 6 ft × $^{1}/_{8}$ in., packed with 5% Silicone-30, DMCS treated on Chromosorb G, temperature 86°), revealed the presence of ethyl isobutyrate (**22**), ethyl 2,2,4-trimethyl-3-oxovalerate (**24**), diisopropyl ketone (**25**), and 2,4,4,6-tetramethyl-3,5-heptanedione (**26**).

Neutralization of the aqueous layer with 6 *N* HCl was followed by an ether extraction. The organic extracts were dried ($MgSO_4$), filtered, and distilled to give a yellow liquid which was shown to contain only isobutyric acid by glpc analysis.

Registry No.—**1,** 3173-79-3; **7,** 10472-28-3; **8,** 10472-29-4; **11,** 10472-30-7; **12,** 918-71-8; **13,** 10472-32-9; **14,** 10472-33-0; **18,** 10472-34-1; **19,** 10472-36-3; **20,** 10472-35-2; **21,** 778-18-7; **22,** 3763-08-4; **24,** 4447-64-7; **26,** 5011-63-2; methylmagnesium iodide, 917-64-6; ethylmagnesium iodide, 10467-10-4; isopropyllithium, 1888-75-1; isopropylmagnesium bromide, 920-39-8; phenylmagnesium bromide, 100-58-3.

Acknowledgment.—The authors are deeply indebted to Claude H. Dungan (Monsanto Chemical Co.) for the molecular weights of **7** and **8** and the 100-Mc nmr analysis of **8**.

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[20] V. I. Traynelis, W. L. Hergenrather, H. J. Hanson, and J. A. Valicenti, *J. Org. Chem.*, **29**, 123 (1964).

[21] R. H. Hasek, E. U. Elam, J. C. Martin, and R. G. Nations, *ibid.*, **26**, 700 (1961).

[22] J. L. E. Erickson, F. E. Collins, Jr., and B. L. Owen, *ibid.*, **31**, 480 (1966).