ester and butenolide (split band of equal intensities at 5.60 and 5.66 μ). Gas phase chromatography under a standard set of reference conditions[20] also showed a 1:1 mixture of butenolide and pseudo ester.

When the equimolar mixture of butenolide and pseudo ester, from above, was distilled through a 2-ft. Podbielniak type column, there was a forerun of 0.136 g., then there was collected 0.745 g. of butenolide, b.p. 119°/1 mm.; infrared absorption at 5.67 μ (very weak absorption at 5.93 μ); in the ultraviolet, λ_{max} 213 mμ, ϵ 12,000. Combustion analysis of several samples gave persistently low values for carbon; highest values were obtained by slow burning at relatively high furnace temperature.

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.5; H, 10.2. Found: C, 72.6, 71.1, 72.6; H, 9.9, 9.5, 10.1.

The n.m.r. spectrum, recorded on a Varian instrument, yielded the following bands:

τ	Relative area	Assignment
9.02 (split)	1	$-CH_3$ (terminal)
8.58 (broad)	3.2	$-CH_2-$
8.12	1	$-CH_3$ (β)
7.93	1	$-CH_3$ (α)
5.64 (split)	0.3	$\underset{\vert}{-CH}-O$

Assignment of the higher field band to the β-methyl is based on the reported investigation[21] of tiglic and related acids.

B. **Pseudo Ester.**—The acid chloride was prepared as described in method A, except that stirring at room temperature was continued for only 25 min., and the product was stored at 0° until it was added to methanol and sodium carbonate. After reaction had continued for only 0.5 hr. with methanol, the mixture was diluted with ether and worked up as before (without distillation) to give a 55% yield of an oil with an infrared band at 5.60 μ. Gas chromatographic analysis[20] showed the material to be about 75% pseudo ester, about 2% normal ester, and about 15% butenolide. There was a small band at about 35.5 min. which has not been identified.

Rearrangement of the pseudo ester was carried out by heating a 58-mg. sample of material prepared as above at 40° for 4 hr. with 1.5 ml. of a 10% solution of sulfuric acid in methanol. The reaction mixture was diluted with ether, washed with water, and dried. Removal of solvent left an oil (55 mg.) which showed carbonyl absorption at 5.76, 5.83 μ, with a shoulder at 5.67 μ. Gas chromatographic analysis[20] showed only two bands, one at 27 min. (normal ester) containing about 90% of the area, and a small band at 41 min. (butenolide III).

Butenolide III from Normal Ester.—A solution of 100 mg. of methyl 2,3-dimethyl-4-oxodecanoate was prepared in carefully dried methanol which was approximately 1 *N* in sodium methoxide. After this mixture had been heated at 45° for 3 hr. in a nitrogen atmosphere, it was cooled in an ice bath and the pH was reduced to about 5.5 with dry methanol which was about 2 *N* with anhydrous hydrogen chloride. The mixture was then diluted with about 25 ml. of dry ether, sodium chloride was removed by filtration, and solvent was removed at reduced pressure to leave 82 mg. of an oil, which was shown by gas chromatography[20] to consist of about equal amounts of starting material (normal ester) and butenolide III. No other bands were observed. This mixture was easily separated by gas chromatography at 200° on a 15-mm. i.d. × 3-m. column containing 30% high vacuum silicone grease dispersed on Chromosorb P. Fractions collected were 33 mg. of starting material (infrared spectrum and gas chromatography) and 34 mg. of butenolide III (infrared and ultraviolet spectra, gas chromatography).

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[20] For analysis of the mixtures encountered in these reactions, chromatography was carried out at 130° on a 1/4 in. × 5 ft. column of 10% high vacuum silicone grease dispersed on 40–60 mesh Chromosorb P, with helium flow rate of 70 ml./min. Under these conditions, retention times were as follows: normal ester, 27 min.; pseudo ester, 33 min.; butenolide, 41 min. On some occasions, material in bands was collected and identity checked by use of the infrared spectrum.

[21] R. R. Fraser, *Can. J. Chem.*, **38**, 549 (1960).

Epimerization of *s*-Dimethylsuccinic Acids and Derivatives. Cadmium Reactions on the Ester Acid Chlorides

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Convenient methods are described for securing *meso* and *racemic* *s*-dimethylsuccinic anhydrides, whose purity may be verified by gas phase chromatography. The isomeric anhydrides may be converted to isomerically pure half esters and diesters. Epimerization does not occur at a significant rate under acidic conditions. The half esters may be converted to ester acid chlorides, with 10–15% epimerization, as determined by conversion of the ester acid chlorides to diesters, whose composition may be determined by gas chromatography. The ester acid chlorides are slowly epimerized on standing at room temperature, to yield an equilibrium mixture of the diastereo isomers containing slightly more than half of the *threo* isomer. Equilibration of the *s*-dimethylsuccinic acids by heating with hydrochloric acid also gives equilibration slightly in favor of the *racemic* form (same geometry as *threo* form). Reaction of either isomeric ester acid chloride with dihexylcadmium reagent yields a keto ester of the same geometry as was the ester acid chloride, with little or no epimerization. Separation of isomeric keto esters by gas chromatography was possible only in the case of the methyl ketones; however, structure could be determined by Baeyer–Villiger oxidation of the keto esters and transesterification to the dimethyl *s*-dimethylsuccinates. Ratio of secondary to primary alkyl migration, in oxidation with perfluoroperacetic acid, was only 2:1. Catalytic or chemical reduction of the isomeric keto esters yielded mixtures of four lactones, separable into three bands in gas chromatography. Structures were assigned to the two lactones appearing as single components of two of the chromatography bands, on the basis of origins of the lactones, relative rate of formation from the hydroxy acids, and isomers related by epimerization.

In view of the considerable enolization noted in reaction of α-chloro acid chlorides with organocadmium reagents,[2] it has been presumed that epimerization at the α-position is likely to occur in ketone syntheses utilizing the cadmium reagents. For example, in the preparation of optically active α-phenylethyl methyl ketone,[3] it was suggested that the highly variable amount of racemization observed (0–90%) occurred during reaction of hydrotropyl chloride with dimethylcadmium reagent. It was not determined, however, whether racemization might be occurring during preparation and/or storage of the acid chloride. Such equili-

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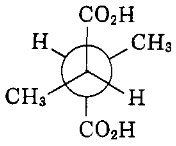
[1] Recipient of a National Science Foundation Summer Fellowship, 1960; a U. S. Rubber Co. predoctoral Fellowship, 1959–1960; a Procter and Gamble Co. predoctoral Fellowship, 1960–1961.

[2] J. Cason, *J. Am. Chem. Soc.*, **68**, 2078 (1946).

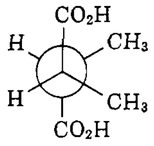
[3] K. Mislow and J. Brenner, *ibid.*, **75**, 2318 (1953).

brations in presence of thionyl chloride have been reported.[4] In connection with recent investigations,[5] involving the synthesis of keto esters, we have examined conditions for epimerization at the several stages of synthesis from *s*-dimethylsuccinic acids to 2,3-dimethyl-4-oxo esters. It may be said at the outset that there appears to be little, if any, epimerization during the normal procedure for reaction of an acid chloride with an organocadmium reagent.

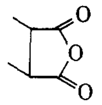
A mixture of the diastereoisomeric *s*-dimethylsuccinic acids may be readily obtained *via* alkylation of diethyl methylmalonate with ethyl α-bromopropionate. When the intermediate tricarboxylic acid was decarboxylated with a minimum of heating, an approximately 1:1 ratio of the *meso*- and *racemic*-dimethylsuccinic acids was obtained. With more vigorous heating, as much as 86% of the product was the *racemic* isomer. Inspection of Newman projections for the *meso* (I) and *racemic* (II) forms of this acid suggests that the *meso* form would be the more stable (however, see below). There is little doubt that the preponderance of *racemic* isomer obtained on heating results from formation and epimerization of the anhydrides (III and IV), which are subsequently hydrolyzed during work-up of the reaction mixture. The higher melting and less soluble *meso* acid is readily isolated; therefore, the *meso* isomer is best obtained as the diacid, from preparations which have been heated a minimum amount for decarboxylation. On the other hand, the *racemic* anhydride is higher melting and less soluble than the *meso* anhydride; thus the *racemic* isomer is best obtained at the anhydride stage.



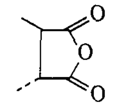
I (*meso*)



II (*racemic*)

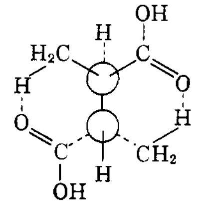


III (*meso*)

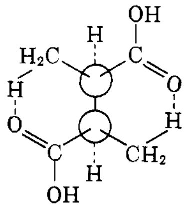


IV (*racemic*)

Since pure *meso* anhydride may be obtained readily only from the pure *meso* acid, it is often desirable to convert the *racemic* acid to the *meso* form. As would be predicted from inspection of Newman projections (I and II) of the acids, Bone and Perkin[6] have reported that the *racemic* acid is converted to the *meso* form by heating at 180° with concentrated hydrochloric acid. Linstead and Whalley,[7] however, were able to obtain only 5% conversion of *racemic* to *meso* by heating under reflux for forty hours with concentrated hydrochloric acid. More recently, Eberson[8,9] has studied the actual equilibrium involved and found that the *racemic* isomer actually predominates, although by a narrow margin (2–5%). Our findings are in agreement with Eberson, in that only 20–40% of the *meso* isomer could be isolated after equilibration at 180° with hydrochloric acid. A reasonable explanation of the similar stabilities of the two isomers (not predicted from inspection of formulas I and II) may be based on the previous proposal that carboxylic acids actually exist in substantial measure[10] as cyclic structures involving weak hydrogen bonding with a hydrogen on the γ-carbon. Semiprojections of the two forms (V and VI) suggest similar stabilities. Eberson[8,9] has suggested a different type of hydrogen bonding involving a seven-atom ring.



V (*meso*)



VI (*racemic*)

Pure samples of the isomeric anhydrides (melting point and gas chromatography) could be converted by reaction with methanol to isomerically pure half esters. The small amount of diester formed in this reaction was also isomerically pure. In addition, a sample of the *meso* diester was not converted to a detectable amount (gas chromatography) of the *racemic* form after ten hours under reflux with 10% sulfuric acid in methanol. Thus, epimerization is extremely slow under acidic conditions.

Although the *s*-dimethylsuccinic acids, their half esters, and diesters are not readily epimerized under acidic conditions, a small amount of equilibration does occur during formation of the ester acid chlorides, and epimerization continues on standing at room temperature (Table I). In this derivative, also, equilibration is slightly in favor of the *threo* form (same geometry as the *racemic* form). The several samples of freshly prepared ester acid chlorides, which were used for synthesis of keto esters, contained 10–15% of the product of epimerization.

TABLE I

ISOMERIZATION OF METHYL ESTER ACID CHLORIDES OF *s*-DIMETHYLSUCCINIC ACIDS

Half ester used	Storage period, days	Diesters, %[a]	
		Racemic	*meso*
erythro	1	15	85
	26	52	48
	56	59	41
threo	1	90	10
	30	62	38

[a] Distribution between the diesters formed on reaction of the ester acid chlorides with methanol after the storage period; analysis by gas chromatography.

The keto ester formed by reaction of dihexylcadmium reagent with either isomeric ester acid chloride of *s*-dimethylsuccinic acid always had the same properties, and numerous partitioning agents failed to effect any separation of isomers by gas chromatography. The infrared spectra of the keto esters from isomeric

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[4] J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 5445 (1960); W. G. Dauben and E. Hoerger, *ibid.*, **73**, 1504 (1951).

[5] J. Cason and F. J. Schmitz, *J. Org. Chem.*, **27**, 552 (1962).

[6] W. A. Bone and W. H. Perkin, *J. Chem. Soc.*, 253 (1896).

[7] R. P. Linstead and M. J. Whalley, *ibid.*, 3722 (1954). These authors were the first to correlate the various names applied to these acids in earlier literature, and to assign the proper nomenclature to the high and low melting forms.

[8] L. Eberson, *Acta Chem. Scand.*, **13**, 40 (1959).

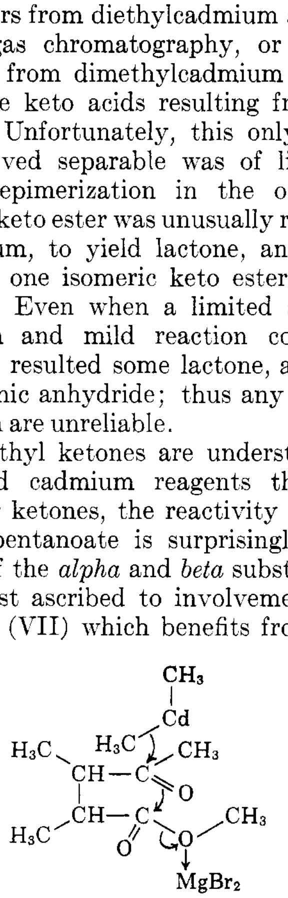
[9] L. Eberson, *ibid.*, 203 (1959).

[10] J. Cason and G. Sumrell, *J. Org. Chem.*, **16**, 1177 (1951).

ester acid chlorides were essentially identical except for a small difference in the relative intensities of two prominent bands at about 8.3 and 8.6 μ. The keto ester from the *erythro* isomer had a slightly more intense band at 8.6 μ, whereas this band was slightly weaker in the ester from the *threo* isomer. In the isomeric diesters, the band near 8.6 μ was much stronger in the *meso* isomer, slightly weaker in the *racemic* isomer. In similar relation, the *erythro* ester acid chloride exhibited bands of similar intensity at 8.31 and 8.56 μ, whereas the *threo* isomer exhibited a strong band at 8.32 μ and a much weaker band at 8.63 μ. It follows that the keto esters from the isomeric acid chlorides were probably the expected isomers to a major extent, but no quantitative determination of composition could be based on the infrared spectra.

The keto esters from diethylcadmium also proved inseparable by gas chromatography, or other means; however, those from dimethylcadmium proved separable, as did the keto acids resulting from hydrolysis of the esters. Unfortunately, this only pair of keto esters that proved separable was of little value for estimation of epimerization in the organocadmium reaction. The keto ester was unusually reactive toward dimethylcadmium, to yield lactone, and there is the possibility that one isomeric keto ester might be the more reactive. Even when a limited amount of dimethylcadmium and mild reaction conditions were used, there still resulted some lactone, as well as some *s*-dimethylsuccinic anhydride; thus any conclusions as to epimerization are unreliable.

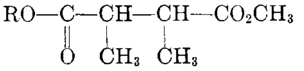
Although methyl ketones are understandably more reactive toward cadmium reagents than the more hindered higher ketones, the reactivity of methyl 2,3-dimethyl-4-oxopentanoate is surprisingly great, especially in view of the *alpha* and *beta* substituents. This reactivity is best ascribed to involvement of a cyclic transition state (VII) which benefits from decrease of



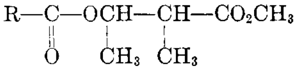
VII

hindrance by dispersion of the sites of attack by the acid and base, as well as formation of the lower energy cyclic structure. An alternate nearly equivalent formulation would involve coordination of the Lewis acid with carbonyl, but direct removal of methoxyl and formation of the five-membered ring with exocyclic double bond seem energetically more attractive. A very high ratio of cyclic products from reactions of succinyl dichloride has been noted previously,[11] and similar types of cyclic transition states have been invoked as the only rational explanation.

To achieve analysis of isomeric composition of the keto esters, recourse was had to degradation. Hypohalite oxidation, followed by esterification, to yield isomeric dimethyl *s*-dimethylsuccinates, proved worthless. The separated *erythro* and *threo* 2,3-dimethyl-4-oxopentanoic acids yielded identical mixtures of the *s*-dimethylsuccinates. The alkaline conditions of the oxidation no doubt caused epimerization *via* enolate ions. In contrast, Baeyer–Villiger oxidation[12] of a 2,3-dimethyl-4-oxo ester gives two products, VIII and IX, depending on whether the primary or secondary group migrates, and configuration of the asymmetric centers should be retained. Even the group that migrates has been shown to retain its configuration.[12] Transesterification of VIII with methanol


$$\mathrm{RO{-}\underset{\underset{O}{\|}}{C}{-}\underset{CH_3}{\underset{|}{CH}}{-}\underset{CH_3}{\underset{|}{CH}}{-}CO_2CH_3}$$

VIII


$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}O\underset{CH_3}{\underset{|}{CH}}{-}\underset{CH_3}{\underset{|}{CH}}{-}CO_2CH_3}$$

IX

gives the dimethyl *s*-dimethylsuccinates which may be analyzed by gas phase chromatography. Although secondary alkyl groups have been reported to have a substantially greater migratory aptitude than primary alkyl groups,[12,13] the reaction was applied anyway, since a very small yield of the desired product may be analyzed by gas phase chromatography. Actually, the ratio of secondary to primary migration proved to be only about 2:1, when trifluoroperacetic acid was used as oxidant.[13] Definitive results were obtained when the oxidation and transesterification sequence was applied to the methyl 2,3-dimethyl-4-oxodecanoates (Table II). Very little starting material survived the reaction, so selective rates of reaction with the two isomers are eliminated as a disruptive factor. Since 10–15% epimerization occurs in preparation of the acid chlorides (*cf.* Table I), equilibration during the organocadmium reaction is shown to be a minor effect at most.

TABLE II

BAEYER–VILLIGER OXIDATION OF ISOMERIC METHYL 2,3-DIMETHYL-4-OXODECANOATES

Isomer[a] oxidized	—Products,[b] %— Un-changed, %	Heptan-oate	Diesters	Isomer distribution,[c] % *threo*	*erythro*
threo	4–5	24	13	84	16
erythro	2–4	29	13	21	79

[a] Related to isomeric ester acid chloride used for reaction with dihexylcadmium reagent. The *threo* acid chloride was used shortly after preparation, and contained 10–15% of the epimer, the *erythro* acid chloride had been stored 9 days and contained 20–25% of the epimer. [b] Refers to over-all yield of methyl heptanoate formed by transesterification of IX, and of isomeric diesters formed by transesterification of VIII. Yields were calculated by comparison of response areas observed in gas chromatography of reaction products with the areas observed on injection of known amounts of the pure compounds. Chromatography was at 90° for analysis of the product esters, at 130° for determination of starting material; 5-ft. column, 1/4-in. diam., packed with 10% high vacuum silicone grease dispersed on 40–60-mesh Chromosorb P. For representative recorder tracings, *cf.* Experimental, Fig. 2. [c] Refers to percentage composition of the product diesters, as determined by gas chromatography according to procedure described in footnote *b*. In a run under conditions giving a larger percentage of recovered starting material, distribution between the isomeric diesters was similar.

In further study of the 2,3-dimethyl-4-oxodecanoates, lactones were obtained by reduction. Although the isomeric lactones were separated only in quantities large enough for spectral determinations, certain of their chemical properties could be studied effectively

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(11) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1668 (1958).

(12) C. H. Hassall, *Org. Reactions*, **9**, 73 (1957).

(13) M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Am. Chem. Soc.*, **80**, 6393, 6398 (1958).

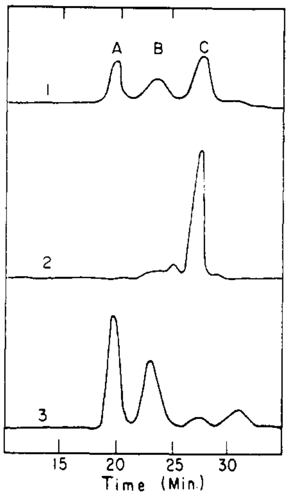
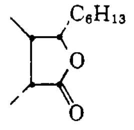


Fig. 1.—Gas phase chromatography of isomeric lactones on 5-ft., 1/4-in. diameter column packed with 10% high vacuum silicone grease dispersed on 40–60 mesh Chromosorb P; temperature, 140°; helium flow rate, 80 ml./min.

Curve 1: product of next to last reaction, Table III.
Curve 2: hydrogenation of butenolide XIV.
Curve 3: first reaction in Table III.

by use of analysis by gas chromatography. There was established the formation of isomeric lactones consistent with expectations based on the assigned configurations of the keto esters. If no epimerization occurs during the reduction, the *threo* isomer of the keto ester would yield lactones X and XI, while the *erythro* isomer would yield XII and XIII; however, each sample of keto ester contained 15–20% of the epimer (*cf.* Table II). Reduction of either of the isomeric keto esters gave a product exhibiting only three bands in gas chromatography (Fig. 1, curve 1); however, the second of these bands obviously represents two compounds with very slightly different retention times. Band *B* is wider than band *C*, in spite of the fact that the former is of smaller area and of shorter retention time. Material collected from each of these bands showed carbonyl absorption only at 5.62 μ, the position expected for a γ-lactone. The ratio of areas in the three lactone bands, on chemical and catalytic reduction of the isomeric keto esters, is summarized in Table III. It may be noted that the relative abundance of isomers is the same for the two types of reduction, and this suggests that no major amounts of epimerization have occurred, as do the differences in product composition for the two stereoisomeric keto esters.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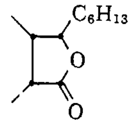
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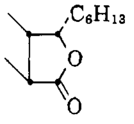

XII

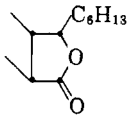

XIII

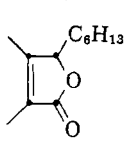
TABLE III

LACTONES FROM REDUCTION OF ISOMERIC METHYL 2,3-DIMETHYL-4-OXODECANOATES

Isomer	Reagent	Band area of lactones, % A	B	C	Total yield, %
threo	$NaBH_4$[a]	54	40	6	92
	H_2, Pt[b]	63	26	11	78
erythro	$NaBH_4$	23	33	44	77
		27	28	45	85
	H_2, Pt[b]	20	33	47	62

[a] In this reaction only, a fourth band was observed in gas chromatography (*cf.* Fig. 1, curve 3). This band, representing about 12% of the total area, has the retention time of the butenolide XIV, which has been obtained by treatment of the keto ester with methoxide.[5] Percentages recorded for the lactone bands are based on total area of only those bands. [b] Hydrogenation was in glacial acetic acid at room temperature and a pressure of about 45 p.s.i.; time required was 32–39 hr.

In order to accomplish assignment of the stereoisomeric lactones (X–XIII) to the gas chromatography bands observed, recourse was had to hydrogenation of the butenolide, XIV, whose structure has been rigorously assigned.[5] Recent studies on hydrogenation of cyclic olefins have shown[14] that use of platinum catalyst in acetic acid results in a dominance of *cis*-addition, with very little double bond migration prior to reduction. Furthermore, hydrogenation of 2,3-dimethyl-1-cyclohexene gave as major product the *cis*-1,2-dimethylcyclohexane (70–80% of the saturates). This result was rationalized on the basis of the expectation that the unsaturated molecule would be preferentially adsorbed on the catalyst from the least hindered side. In analogous fashion, the butenolide XIV would be expected to yield lactone XIII as the dominant product of hydrogenation. Gas chromatography of the lactone from this hydrogenation showed it to consist almost exclusively of a single product (Fig. 1, curve 2) of the same retention time as band *C*, curve 1.


XIV

For verification of the assignment of band *C*, Fig. 1, to lactone XIII, the rate of formation of this lactone by cyclization of the hydroxy acid was compared with that of the other isomers (X–XII). Structure XIII should exhibit the slowest rate of formation, as is shown by the data in the following chart to be the fact for the lactone in band *C*:

Lactone mixture bands
A *B* *C*
45% 32% 23%

(1) ^-OH heat 0.5 hr. →
(2) H^+, to pH 3. 0.5 hr. at room temp.

Lactone product bands
A *B* *C*
55% 39% 6%

↓

Acid product

↓ 80° at pH 3 for 1 hr.

Lactone product bands
A *B* *C*
0% 66% 34%

Thus, the lactone corresponding to band *C* is formed at the slowest rate, while that corresponding to band *A* is formed at the fastest rate; therefore, assignment of lactone XIII to band *C* is confirmed.

It may be noted in Table III that the dominant lactone from reduction of the *threo* isomer of the keto

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(14) S. Siegel and G. V. Smith, *J. Am. Chem. Soc.*, **82**, 6082 (1960).

ester is that corresponding to band *A;* therefore, band *A* must be ascribed to either lactone X or XI (*trans* structure for the methyl groups). Since XI would be formed by epimerization from XIII, a choice may be made on this basis. When lactone XIII was heated with methanolic sodium hydroxide, and lactones were isolated from the acidified reaction mixture after heating, gas chromatography showed a quantitative recovery of lactones distributed equally between bands *B* and *C*. It follows that band *A* cannot represent structure XI, therefore must be assigned to lactone X; this leaves lactones XI and XII responsible for band *B*. The facile cyclization of the hydroxy acid to give lactone X, with completely staggered arrangement of substituents, stands in confirmation of assignment of this lactone to band *A*. The distribution of lactones obtained by reduction of the isomeric keto esters also stands in agreement with the structures assigned to the keto esters on the basis of the products of Baeyer–Villiger oxidation.

Experimental[15]

***s*-Dimethylsuccinic Acids.**—Diethyl β-carbethoxy-α,β-dimethylsuccinate was prepared as previously described[16] in 83% yield, b.p. 118–120°/2 mm. The triester was hydrolyzed with 6*N* hydrochloric acid,[16] the reaction mixture was concentrated by distillation at atmospheric pressure, and the residue was heated for 1.5 hr. to effect decarboxylation. With decarboxylation at 190–200°, the total yield was about 70% and the product was about 55% *meso* and 45% *racemic*. With decarboxylation at 190–230°, total yield, 92%; 15% *meso* and 85% *racemic*. Separation of isomers in a run utilizing 242 g. of triester, and decarboxylated at 190–230° is outlined.

The residue from decarboxylation was heated under reflux for 3 hr. with 600 ml. of concd. hydrochloric acid, then allowed to stand overnight at room temperature. The crystallizate of 31.5 g. (m.p. 160–210°) was recrystallized from 155 ml. of 10*N* hydrochloric acid to yield 16.6 g. of pure *meso* acid, m.p. 204–209°.[17] Subsequent crops were 3.8 g. (m.p. 123–130°), 2 g., and 5.4 g. (residue from evaporation). The mother liquor (600 ml. concd. hydrochloric acid) from the initial crystallization of *meso* acid was decolorized with charcoal, reduced to a 500-ml. volume, and allowed to deposit crystals at about 20° for several hours; weight 33.1 g., m.p. 121–126°.[17] An additional crop of relatively pure *racemic* isomer was collected after 24 hr. at 0°; weight 12.9 g., m.p. 120–125°. Evaporation of the mother liquor to dryness and crystallization of the residue (41.6 g.) from 125 ml. of water yielded 10.3 g. of additional *racemic* isomer, m.p. 120–126°. The residue from evaporation of the final mother liquor weighed 28.2 g., m.p. 73–79°.

Equilibration of *s*-Dimethylsuccinic Acids.—In a typical run, a mixture of 5 g. of mostly *racemic*-dimethylsuccinic acid and about 35 ml. of concd. hydrochloric acid was heated in a sealed tube at 180–200° for 8–10 hr. The crystallizate recovered by filtration from the cooled reaction mixture consisted of pure *meso* isomer, weight 1.5 g., m.p. 204–210°. Additional crops (total of about 3 g.) were always low-melting, usually in the range 118–130°. In several runs, the highest recovery of *meso* isomer was 39%.

***meso*-Dimethylsuccinic Anhydride (III).**—Following a procedure similar to that of Bone and Perkin,[6] a mixture of 10.8 g. of pure *meso*-dimethylsuccinic acid (m.p. 204–210°) and 15 ml. of acetyl chloride was allowed to stand at room temperature for 1.5 hr., then heated at 55–60° for 3 hr. Excess acetyl chloride and most of the acetic acid were distilled from the reaction mixture at reduced pressure, and the residue was allowed to crystallize while standing in a desiccator with solid potassium hydroxide at about 100 mm. Recrystallization from dry ether, after charcoal treatment, yielded 5.15 g. (40%) of pure *meso* anhydride, m.p. 36–37.2° (lit.,[6,7] m.p. 39–40°, 42–43°). Gas phase chromatography revealed only a trace of the *racemic* isomer.

***racemic*-Dimethylsuccinic Anhydride (IV).**—The previously described procedure was applied to 48.4 g. of the *racemic* acid (m.p. 121–126°). Distillation of the reaction mixture at reduced pressure was continued until solid appeared in the Claisen head, then the residue (41.6 g.) was crystallized from 800 ml. of dry ether to yield 24.3 g. (57%) of pure *racemic* anhydride, m.p. 87.5–88.0° (lit.,[7,18] m.p. 89°, 87–88°).

Pure samples of the *racemic* anhydride may be obtained from samples of acid containing considerable of the *meso* isomer. In such preparations, the anhydride is best crystallized from carbon tetrachloride (8 ml. per gram of anhydride), a solvent in which the *meso* isomer is preferentially soluble.

Methyl Hydrogen *erythro*-Dimethylsuccinate. A. From Diacid.—A mixture of 7.4 g. of pure *meso*-dimethylsuccinic acid (m.p. 200–205°), 5.5 ml. of methanol, 15 ml. of dibutyl ether, and 7.5 ml. of conc. hydrochloric acid was heated with swirling until the mixture became homogeneous (20 min.). The reaction mixture was then heated under reflux for 2.75 hr. and finally fractionally distilled through a 2-ft. Podbielniak type column with a partial reflux head. The yield of diester, b.p. 71–73°/7 mm., was 2.19 g. (25%), and the half ester, b.p. 111–113°/4 mm., amounted to 2.47 g. (31%). The remainder of the material was unchanged diacid and intermediate fractions. The diester was shown by gas chromatography to be isomerically pure. The half ester solidified on standing, m.p. 38–43°; however, after it had stood for several days in a desiccator the m.p. was 47–49°; so polymorphism seems probable (lit.,[19] m.p. 45–47°).

B. From Anhydride. A solution of 9.9 g. of *meso*-dimethylsuccinic anhydride (m.p. 36.0–37.2°) in 3.5 ml. of methanol was heated at 70–80° for 1.75 hr., at which time gas chromatography of a sample of the reaction showed consumption of all the anhydride. When 50 ml. of hexane was added to the cooled solution, the reaction mixture set to a mass of crystals. After the mixture had been warmed to effect solution, it was allowed to stand overnight at room temperature, then the white crystals were collected by suction filtration, washed, and dried; yield 10.1 g. (74%), m.p. 46.0–47.5°. The equivalent weight of this sample was determined as 155 (calcd. for $C_7H_{12}O_4$: 160). An additional 1.4 g. of impure half ester could be obtained from the mother liquor.

Methyl Hydrogen *threo*-Dimethylsuccinate.—In contrast with the *erythro* isomer, this isomer tends to lose methanol when distillation is attempted, so that the principal product of distillation is the anhydride. That the anhydride is converted to half ester prior to distillation was established by gas phase chromatography on the undistilled reaction mixture. This half ester may be readily isolated by crystallization, however.

Using 15.4 g. of *racemic*-dimethylsuccinic anhydride, the half ester was formed as described for the *erythro* isomer, and the hexane solution was allowed to crystallize overnight in the refrigerator. The first crop of crystals weighed 13.1 g., m.p. 36–37.5°, and a second crop of 1.7 g. had m.p. 33–36.5° (total yield, 77%). The best sample obtained by recrystallization had m.p. 37–37.8°, equivalent weight, 159 (calcd. for $C_7H_{12}O_4$, 160) (lit.,[19] m.p. 35–37°).

Acid Chlorides of Methyl Hydrogen Dimethylsuccinates.—A solution of 12.25 g. of pure isomeric half ester in 11 ml. of purified thionyl chloride was allowed to stand at room temperature for 9 hr., then heated at 40° for 5 hr. The excess thionyl chloride was removed at reduced pressure, and the residual acid chloride used for further experiments. In the infrared, both isomers had carbonyl bands at 5.60 and 5.75 μ; the *erythro* isomer exhibited a pair of bands of nearly equal intensity, about three-fourths the intensity of the carbonyl bands, at 8.31 and 8.56 μ, with the former very slightly the stronger; the *threo* isomer had a band at 8.32 μ about equal in intensity to that band in the *erythro* isomer, but the band at 8.63 μ was quite weak.

For analysis of the isomer content of the ester acid chlorides, a small sample was allowed to react at 0° with a large excess of methanol, then the isomeric diesters were determined by gas

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[15] Infrared spectra were determined on an Infracord. Microanalytical determinations were by the Microanalytical Division, Department of Chemistry, University of California. Analytical gas chromatography was on 1/4-in. steel columns in an Aerograph instrument and utilizing a 1-mv. span recorder; separations on larger glass columns used locally built apparatus utilizing a thermistor detector and a 10-mv. span recorder. Complete tracings of the infrared spectra, as well as many gas chromatography tracings, may be found in the Ph.D. thesis of Francis J. Schmitz, University of California, Berkeley, 1961.

[16] J. Cason, G. Sumrell, and R. S. Mitchell, *J. Org. Chem.*, **15**, 857 (1950).

[17] Eberson[8] has reported the pure *meso* isomer to melt at 197–210°, and the *racemic* isomer to melt at 120–127°.

[18] C. A. Bischof and E. Voit, *Ber.*, **23**, 638 (1890).

[19] L. Eberson, *Acta Chem. Scand.*, **13**, 213 (1959).

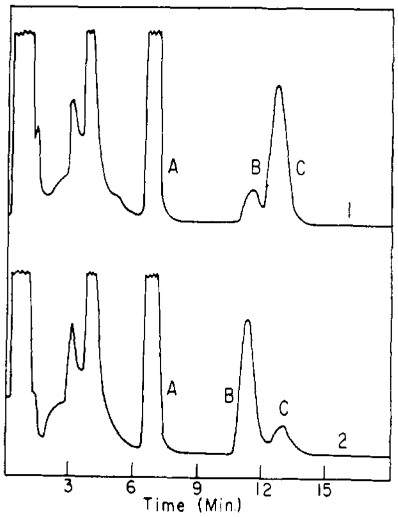

Fig. 2.—Gas phase chromatographic analysis of products from trifluoroperacetic acid oxidation of isomeric keto esters, followed by transesterification with methanol. Same chromatography column as described for Fig. 1; temperature, 90°; helium flow rate, 90 ml./min.

Curve 1: products from methyl *threo*-2,3-dimethyl-4-oxodecanoate.
Curve 2: products from *erythro* isomer.
Band assignments: *A*, methyl heptanoate; *B*, dimethyl *meso*-dimethylsuccinate; *C*, dimethyl *racemic*-dimethylsuccinate. The initial off-scale band is solvent; large bands at 3–5 min. not identified, but one of them is probably heptanol. An attenuated recording was used for determining area of band *A*.

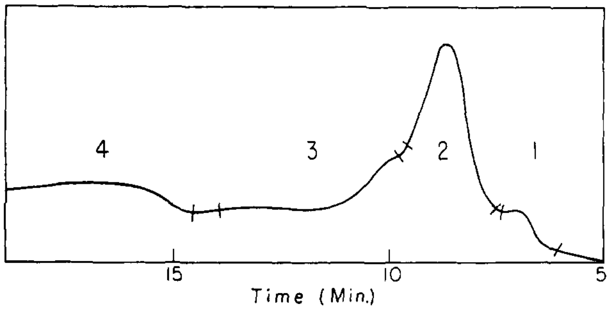

Fig. 3.—Gas chromatography of reaction products in synthesis of isomeric methyl 2,3-dimethyl-4-oxopentanoates. Lines across the tracing indicate where fractions were collected; see Table IV for data on the numbered fractions and description of chromatography column used.

chromatography (*cf.* Fig. 2 for tracings containing these esters). This technique was used to determine the isomeric composition of the ester acid chloride used in each organocadmium reaction. Data on isomerization on standing are assembled in Table I.

Methyl 2,3-dimethyl-4-oxodecanoates were prepared from the isomeric ester acid chlorides by reaction with dihexylcadmium, as previously described.[5] The isomers had the same properties except for the different intensities of the infrared bands at 8.3 and 8.6 μ.

Trifluoroperacetic Acid Oxidation of Isomeric 2,3-Dimethyl-4-oxodecanoates.—A typical oxidation, as applied to each isomer, is described; quantitative results are assembled in Table II.

For preparation of the oxidant, a solution of 0.32 ml. of cold 98% hydrogen peroxide in 1.5 ml. of methylene chloride, contained in a 5-ml. volumetric flask, was cooled in an ice salt bath as there was added, with shaking during about 2 min., 1.93 ml. of freshly distilled trifluoracetic anhydride. After the solution had been shaken for an additional few minutes, it was diluted to 5 ml. with methylene chloride.

To 50 mg. (0.22 mmole) of an isomeric keto ester, dissolved in 0.8 ml. of methylene chloride, was added 0.28 ml. (0.66 mmole) of the cold peracid solution. After this reaction mixture had been heated under reflux for 3 hr. (starch–iodide test for peroxide remained positive), methylene chloride was removed in a stream of air as the flask was warmed at about 50°. Finally, most of the trifluoroacetic acid was removed by warming for about 2 min. at a pressure of 3 mm. The residue was heated under reflux for 20 hr. with 0.8 ml. of methanol containing 10% by weight of sulfuric acid. The cooled solution was diluted with 40 ml. of ether, then washed in sequence with 2-ml. portions of 0.5 *M* carbonate solution, water, and saturated sodium chloride solution. The dried solution was concentrated under a 2-ft. fractionating column, and the final volume was adjusted to 2 ml. Aliquots of this solution were used for qualitative and quantitative analysis by gas chromatography; *cf.* Fig. 2 for representative tracings.

Methyl 2,3-dimethyl-4-oxohexanoate was prepared in 42% yield by reaction of diethylcadmium reagent with the ester acid chloride of *s*-dimethylsuccinic acid (*threo* 62%, *erythro* 38%). No evidence of isomers of the keto ester could be secured by gas chromatography on 1.5- or 3-meter columns; partitioning agents examined were Craig polyester (butanediol succinate), DEGS, polypropylene glycol, tri-*o*-tolyl phosphate, and UCON polar. The infrared spectrum was similar to that of the homologous keto esters, with carbonyl bands at 5.75 and 5.84 μ, and also the prominent characteristic pair of bands at 8.32 and 8.60 μ (latter slightly stronger). When the ester was saponified with alkali, then re-esterified, the 8.60-μ band had become very slightly weaker (ratio of isomers shifted by alkaline saponification). The **keto acid**, obtained by saponification, showed the strong carboxyl band at 5.87 μ, with characteristic carboxyl absorption above 3 μ; however, a shoulder at 5.64 μ indicated a small content of lactol in the acid.

Methyl 2,3-Dimethyl-4-oxopentanoates.—When the cadmium reaction was carried out in the usual way,[5] there resulted a complex mixture which contained some of the desired keto esters, some *s*-dimethylsuccinic anhydride, and another product judged to be α,β,γ-trimethyl-γ-valerolactone. The latter assignment was based on the following evidence: (1) it exhibited a longer retention time in gas chromatography than did the keto esters or the anhydride, (2) infrared absorption was at 5.62 μ, and (3) use of excess of dimethylcadmium gave this substance as principal product. The amount of lactone was reduced by a modified procedure for the organocadmium reaction, as follows.

The organocadmium reagent was prepared in the usual manner *via* the Grignard reagent from 209 mg. of magnesium and excess methyl bromide. To the solution of the cadmium reagent, cooled to 5–10°, was added 1.0 g. of a mixture (60% *threo*) of the isomeric ester acid chlorides. The reaction was continued with stirring for 1.5 hr. at room temperature and 1.75 hr. at 40°, then decomposed by addition of 3 ml. of saturated aqueous ammonium chloride (aqueous washings hydrolyze the keto ester rapidly). The clear benzene solution was decanted from the white paste of salts, then the salts were washed with benzene. A small water layer was immediately separated from the combined benzene extracts, the solution was dried with sodium sulfate, and solvent was removed at reduced pressure to leave 0.62 g. (70%) of total products. In the carbonyl region in the infrared, there were very strong bands at 5.76 and 5.85 μ, and a band of about half their intensity at 5.62 μ.

The infrared spectrum of the crude product, and especially the spectrum of the first fraction in gas chromatography of the crude product, suggested the presence of ester acid chloride or anhydride. Since neither the spectrum nor the gas chromatogram was altered by treatment of the product with methanol for a few minutes, anhydride was indicated. The ester acid chloride reacts completely with methanol at 0° in less than 1 min. Accordingly, the product was heated with methanol for 2 hr. before separation. This treatment diminished the intensity of the 5.62-μ infrared band, removed a band at 10.4 μ characteristic of the anhydride, removed a peak corresponding to *racemic* anhydride from the gas chromatograph, and introduced a broad peak in the gas chromatograph corresponding to methyl hydrogen *s*-dimethylsuccinates. The product resulting from methanol treatment was separated by gas phase chromatography, to give the components included in Table IV. A characteristic tracing from the gas chromatographic separation on the large column is shown in Fig. 3.

The keto ester having the shorter retention time (Fig. 3) is assigned the *threo* configuration, for the characteristic infrared bands at 8.32 and 8.59 μ are of about equal intensity. For the *erythro* isomer, the band at 8.57 μ was considerably stronger than that at 8.30 μ. The *threo* isomer showed strong carbonyl bands at 5.75 and 5.85 μ, the *erythro* at 5.75 and 5.82 μ; neither of these purified samples showed the shoulder at about 5.62 μ.

TABLE IV

SEPARATION OF ISOMERIC METHYL 2,3-DIMETHYL-4-OXOPENTANOATES

Fraction no.	Retention time, min.[a]	Wt. mg., recovered	Identity of component	Yield, %[b]
1	7.0	7	*threo* isomer[c]	2
2	8.6	146	*erythro* isomer[d]	40
3	10, 13	27	Mixture[e]	7
4	16–20	76	Half esters[f]	21

[a] Chromatography was on a 3 m. × 15 mm. o.d. glass column packed with 30% high vacuum silicone grease dispersed on Chromosorb P; temperature 150°; helium pressure 11 cm. of mercury. A sample tracing, from a 15-mg. injection, is shown in Fig. 3. [b] This is the percentage yield in the over-all reaction, based on ratio of material actually recovered multiplied by yield of total product (70%) which was chromatographed. This assumes the same ratio of recovery of injected material for each product, and ignores the different theoretical yields of the by-products. [c] Re-chromatography on an analytical column (1.5-m., 10% high vacuum silicone grease) showed a high degree of homogeneity for this fraction. [d] A part of this fraction was rechromatographed and used for preparation of the 2,4-dinitrophenylhydrazone. [e] Infrared spectrum left nature of components uncertain, but the lactone is included in this fraction. [f] Infrared spectrum and gas phase chromatography indicated a mixture of isomeric half esters contaminated with a small amount of something else.

The **keto acids** obtained by saponification of a mixture of the isomeric keto esters could also be separated by gas chromatography on silicone grease. On a 3 m. × 15 mm. o.d. column containing 30% high vacuum silicone grease, at 150° and a helium pressure of 10 cm. of mercury, retention times of the broad bands were respectively 12.6 and 17.5 min. Since the second band was > 90% of the total, it is assumed that this is the *erythro* isomer, the principal component of the ester mixture. Infrared spectra of the two isomers were very similar except for the fingerprint region, with a strong carbonyl band at 5.84 μ and shoulders at 5.62 and 5.68 μ. The two shoulders may be due to stereoisomeric lactols; it seems unlikely that they are due to impurities, for the same impurities would not be expected in the two gas chromatography bands. Gas chromatography of the two isomers on an analytical column showed a high degree of homogeneity, and equivalent weights by titration were 146 (*threo*) and 145.5 (*erythro*); calcd. for $C_7H_{12}O_3$, 144. These samples were used for hypohalite oxidations described below.

2,4-Dinitrophenylhydrazone of Methyl *erythro*-2,3-Dimethyl-4-oxopentanoate.—The derivative was prepared from 25 mg. of the rechromatographed keto ester (*cf.* Table IV) according to the procedure which has been described for this compound.[20] As previously noted, the original precipitate, m.p. 90–105°, consisted of a mixture of orange prisms and yellow needles. Recrystallization of 3.9 mg. of hand-picked yellow needles from 0.6 ml. of a 1:1 mixture of ether and petroleum ether yielded a mixture of the two forms. A few large orange prisms were hand-picked, m.p. 105–107° (lit.,[20] m.p. 107–109°).

Recrystallization of a sample of hand-picked orange prisms yielded mostly fine yellow needles, m.p. 112–115° (lit.,[20] 121–122°).

Hypohalite Oxidation of Isomeric 2,3-Dimethyl-4-oxo-pentanoic Acids.—In a procedure similar to that which has been used[21] for oxidation of substituents on aromatic nuclei, 35 mg. of pure *erythro* acid in 1 ml. of water was added to 32 μl. of 0.01*N* sodium hydroxide and 9 ml. of 5.25% sodium hypochlorite solution (commercial). The solution was heated with stirring at 85° for 1 hr., then under reflux for 2 hr. Sodium bisulfite solution (20%) was added to the cooled reaction mixture until a negative starch–iodide test was obtained, then 0.1 ml. of concentrated hydrochloric acid was added and the solution was evaporated to dryness on a steam bath. The white residue was ground under successive portions of ether. Evaporation of the ether yielded 24 mg. of crude product, m.p. 111–160°, which was esterified by heating under reflux for 1.5 hr. with 3 ml. of methanol which was 2 *N* with anhydrous hydrogen chloride. Dilution of the reaction mixture with water, recovery of the esters by ether extraction, and gas chromatography of aliquots of the extract showed that the isomeric composition of the s-dimethylsuccinates was 2 parts *racemic*:1 part *meso*. The tracing for the isomeric esters was similar to that shown for these isomers in Fig. 2.

A 9-mg. sample of the pure *threo* acid, oxidized as described above, yielded an essentially identical mixture of *racemic* and *meso* s-dimethylsuccinates. A mixture of isomeric s-dimethylsuccinates has also been reported from hypohalite oxidation in the degradation of monocrotic acid.[22]

Hydrogenation of α,β-Dimethyl-γ-hexyl-Δ^2-butenolide (XIV).—A solution of 27 mg. of the butenolide[5] in 6.5 ml. of glacial acetic acid (distilled from permanganate) was shaken with 105 mg. of commercial platinum oxide catalyst, under 45 p.s.i. hydrogen pressure, for 30 hr. The catalyst was prehydrogenated by shaking under hydrogen pressure in acetic acid for 1 hr. After catalyst had been removed by filtration, the reaction mixture was diluted with 40 ml. of ether, then acetic acid was removed by successive washes with 5-ml. portions of 0.1 *M* carbonate solution. The product recovered from the washed and dried ether solution amounted to 17 mg. of an oil with a single carbonyl band in the infrared at 5.62 μ. Gas chromatography of this product (Fig. 1, curve 2) showed it to consist almost entirely of a single substance with the retention time of one of the isomeric lactones from reduction of methyl 2,3-dimethyl-4-oxodecanoate (curves 1 and 3). Comparison of curves 2 and 3 shows that the butenolide was completely hydrogenated (no chromatography band at about 31 min. in curve 2).

Hydrogenation of the isomeric methyl 2,3-dimethyl-4-oxodecanoates (isomeric compositions similar to those described in Table II) was carried out in the manner described above for the butenolide. The product showed a single carbonyl band in the infrared at 5.61 μ. The compositions determined by gas chromatography of the mixtures of lactones are shown in Table III. Tracings were similar to those shown in Fig. 1.

Sodium Borohydride Reduction of Isomeric Methyl 2,3-Dimethyl-4-oxodecanoates.—In a typical reduction, 100 mg. of keto ester in 5 ml. of isopropyl alcohol was treated with 10 mg. of sodium borohydride, and this solution was heated with stirring at 55° for 7 hr. The reaction mixture was treated with a few drops of glacial acetic acid and stirring was continued for a few minutes, then the mixture was diluted with 50 ml. of ether. The ether solution was washed with 5-ml. portions of 0.3 *M* carbonate solution, with water, and with saturated sodium chloride solution. Evaporation of the dried solution left an oil which was analyzed by gas chromatography as shown in Fig. 1, curves 1 and 3. Each of the gas chromatography bands, *A*, *B*, and *C*, was collected and found to exhibit a single carbonyl band in the infrared at about 5.62 μ.

Hydrolysis and Relactonization of Isomeric Lactones.—A 66-mg. sample of lactones (by gas chromatography, 45% band *A*, 32% band *B*, 23% band *C*) was heated under reflux for 30 min. with a mixture of 0.7 ml. of 1 *N* aqueous sodium hydroxide and 1 ml. of methanol. The original emulsion became homogeneous as soon as boiling temperature was reached. The cooled basic solution was extracted with ether to remove any neutral material (6 mg. recovered), then acidified to pH 2–3 with 2 *N* sulfuric acid. The resultant cloudy solution was diluted with 1 ml. of methanol, then allowed to stand at room temperature for 30 min., after which the resultant two phase solution was diluted with 30 ml. of ether. The ether phase was extracted with small portions of bicarbonate solution until the extracts remained basic. From the washed and dried ether solution was recovered 37 mg. of an oil. Gas chromatographic analysis of this oil showed the following distribution between the lactone bands: *A*, 20._ mg.; *B*, 14.4 mg.; *C*, 2.4 mg.

The bicarbonate extracts of the lactone solution were acidified to pH 2–3, then heated at 80° for 1 hr. By application of the work-up described before, there was recovered 13 mg. of neutral oil distributed among the chromatography bands as follows: *B*, 8.6 mg.; *C*, 4.4 mg. None of band *A* was detected.

Hydrolysis and Relactonization of Lactone XIII.—An 11-mg. sample of lactone XIII, from hydrogenation of butenolide XIV, was hydrolyzed in a manner similar to that described for the mixture of lactones. The cooled reaction mixture was acidified to pH 2–3 and immediately heated to 65° for 30 min. Lactones isolated by the above-described procedure were distributed as follows: band *B*, 5 mg.; band *C*, 5 mg.; no other bands detected.

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(21) D. Neiswender, Jr., W. B. Moniz, and J. A. Dixon, *ibid.*, **82**, 2876 (1960).

(22) R. Adams and E. F. Rogers, *ibid.*, **61**, 2815 (1939).