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ALKYLATIONS AND CERTAIN OTHER REACTIONS OF BUTENOLIDES

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degree of

DOCTOR OF PHILOSOPHY

BY

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Norman, Oklahoma

1964

ALKYLATIONS AND CERTAIN OTHER REACTIONS OF BUTENOLIDES

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To my wife, Carol, for her help and confidence
through this long struggle. And to my two boys
who will reap the benefits from this labor.

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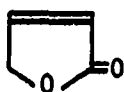
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ALKYLATIONS AND CERTAIN OTHER REACTIONS OF BUTENOLIDES

INTRODUCTION

The butenolide nomenclature will be used throughout this thesis in place of the unwieldy γ -hydroxy- β -butenoic acid lactone or γ -hydroxycrotonic acid lactone nomenclature, which, is now used for indexing purposes to describe this class of unsaturated γ -lactones. The simplest stable member of this class of compounds is $\Delta^{\alpha,\beta}$ -butenolide (I), whereas, the other possible isomer, $\Delta^{\beta,\gamma}$ -butenolide (II), has not yet been isolated.

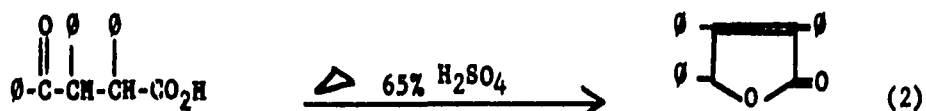
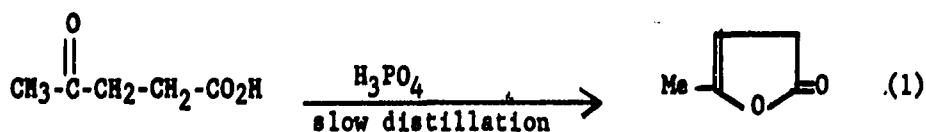


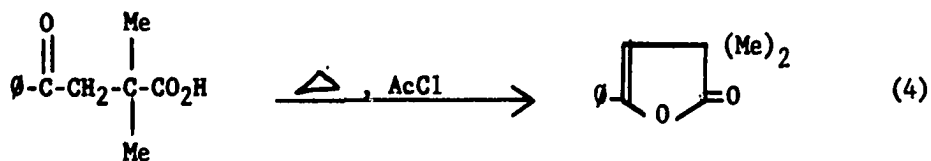
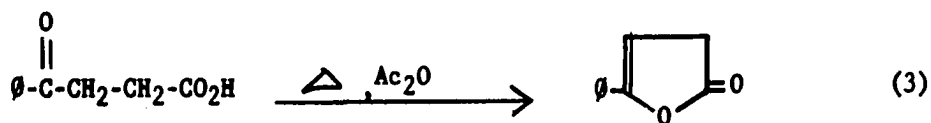
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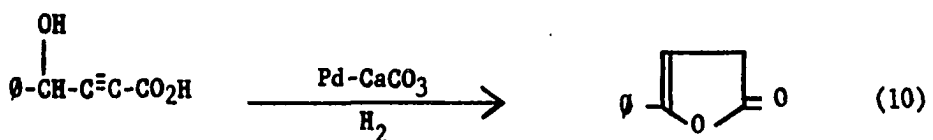
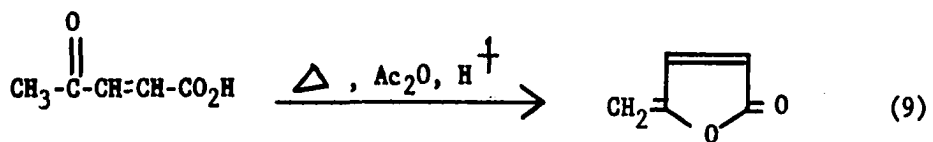
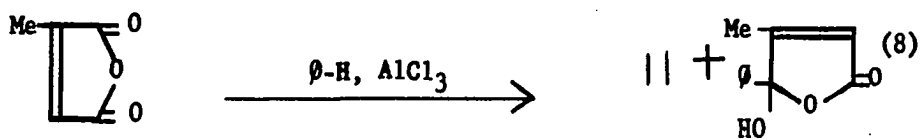
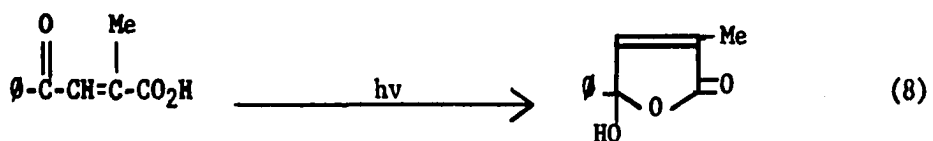
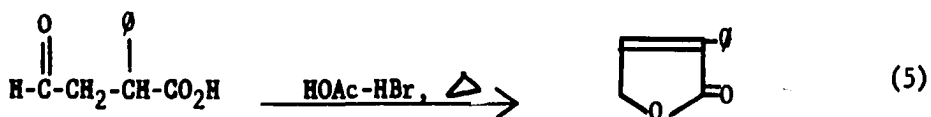
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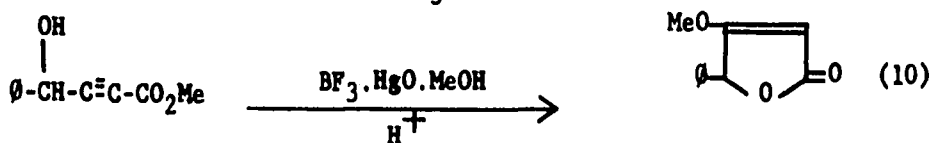
The most general method of preparation of butenolides reported in the literature involves dehydration of the appropriate γ -keto acid as shown in the following equations which serve to illustrate the various procedures available.



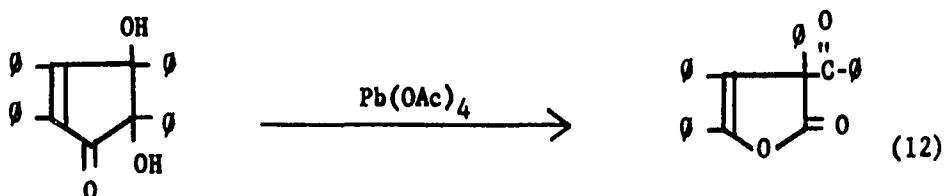
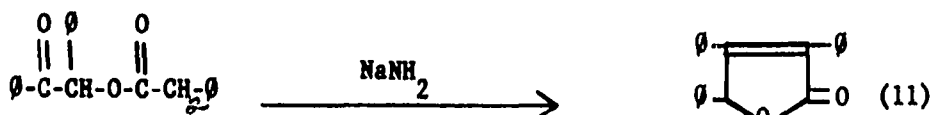


Other less useful methods of preparation, due to the more limited availability of starting materials, are shown in the following equations.





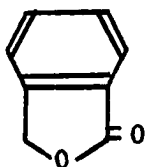
Special preparative methods include the following.



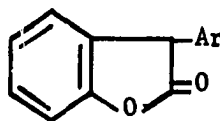
Chemical reactions of the butenolides as reported in the literature include hydrogenations (7,15), Perkin condensations (16,17), Grignard reactions (11,18,19), Diels-Alder reaction (20), Friedel-Crafts reaction (21), lithium aluminum hydride reductions (22,23), halogenations (24), permanganate oxidations (25), oxidative coupling (3), and rearrangements (26). These references serve only to indicate the variety of the reaction types and are not intended to be a complete survey of the chemical literature.

The alkylation and acylation reactions of butenolides were of particular interest to this study. In contrast to the above reaction types these reactions have received comparatively little attention.

Wislicenus (27) reported the ethoxalylolation of the "butenolide type" compound phthalide (III) using sodium ethoxide as the base to give 3-ethoxalylphthalide. Hauser, Tetenbaum and Hoffenberg (28) have carried out a benzylation and benzylation of 3-phenylphthalide using sodium amide as the base to give the 3-substituted derivatives in good yield. In addition the benzylation of phthalide was tried using sodium amide but only a resin was obtained. A review (29) covers a number of alkylations of 3-aryl-2-benzofuranones (IV), also butenolide-like compounds.



III



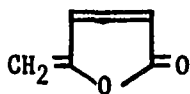
IV

Zaugg and co-workers (30) have also reported the alkylation of 3-phenylphthalide and 3-phenyl-2-benzofuranone using dimethylformamide (DMF) as solvent and noted the failure of these same reactions using benzene and toluene as solvents.

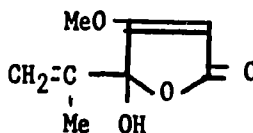
The only attempted acylation reported in the literature on a true butenolide is by Putter and Dilthey (11) who tried to benzoylate α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide, but without success. However, a benzoyl derivative of this compound (which proved to be sensitive to both acids and bases) has been isolated as one of the compounds obtained in the rearrangement of dihydroxytetracyclone (12). This sensitivity may have been a contributing factor in Putter and Dilthey's failure to isolate the desired derivative, since, it could have been destroyed during the course of the reaction or during the work up of the reaction mixture.

The butenolide ring system is represented among the natural

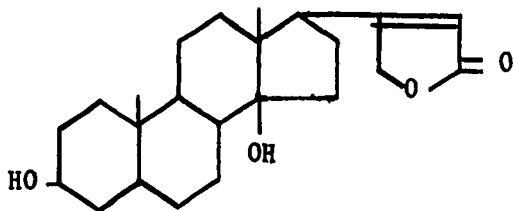
products by protoanemonin (V) (9) which is obtained from extracts of buttercups in the form of a dimer anemonin which gives (V) upon distillation. Raphael (31) prepared penicillic acid (VI) which is also obtained as a mold metabolic product. Fieser (32) gives a very good account of cardiac aglycones of which digitoxigenin (VII) obtained from digitalis serves as an example. The vitamins are represented by the enolic form of vitamin C (L-ascorbic acid) (VIII).



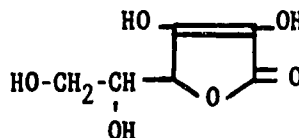
V



VI



VII



VIII

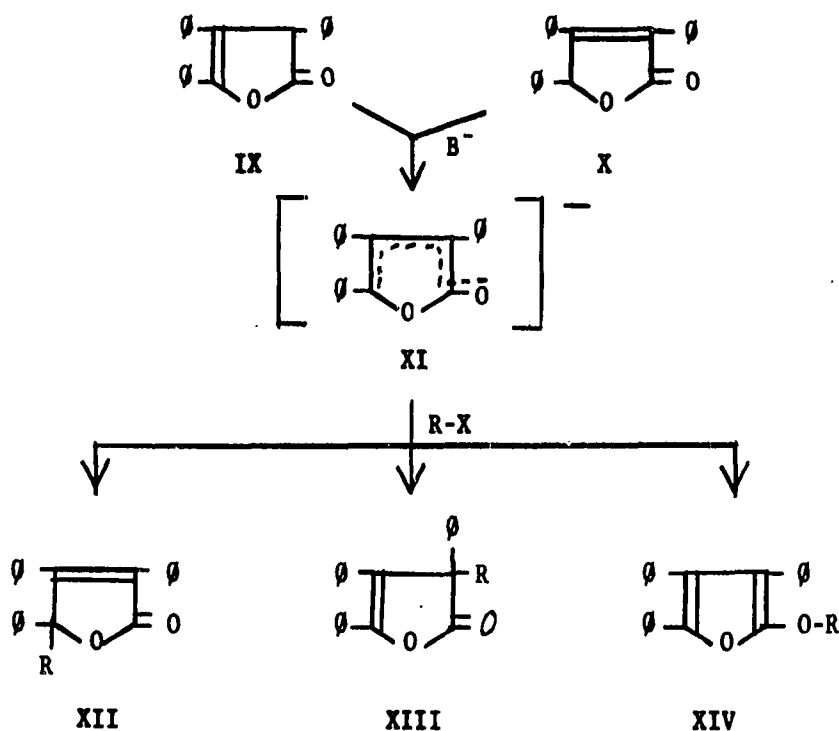
PART I. α, β, γ -TRIPHENYL- $\Delta^{\alpha, \beta}$ -BUTENOLIDE

DISCUSSION

The present chemical literature is devoid of any systematic study of the base catalyzed alkylations and acylations of true butenolides. The present work was undertaken to elucidate the nature of these reactions with respect to the effect of substituents and reaction conditions, including temperature, different solvents, different bases, and different alkylating agents, on the course of the reaction.

The first requirement in the removal of a hydrogen ion from the butenolide molecule is that of a nonnucleophilic base so as to prevent attack at the lactone carbonyl group. The relationship of butenolides to esters indicates that the bases which are suitable for the alkylations of esters would be effective for the same purpose with the butenolides. Suitable bases include alkali alkoxides, alkali amides, alkali hydrides, and bases such as sodium triphenylmethide or lithium butyl. For some other bases that have had a limited or special use, see ref. 29 p. 115-120.

The removal of a hydrogen ion from either an β, γ - or α, β -unsaturated butenolide, represented by (IX) and (X), results in the formation of a carbanion which may be represented by (XI). The alkylation of this ambident anion could, in principle, give (XII), (XIII) or (XIV) under the appropriate conditions.



The availability of α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide (X), with its single reactive hydrogen, was chosen as a model for these reactions.

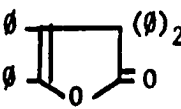
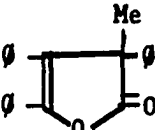
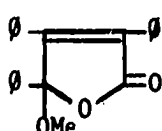
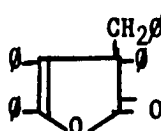
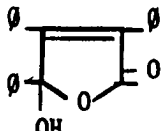
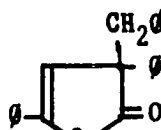
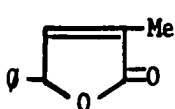
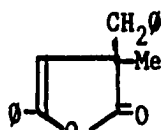
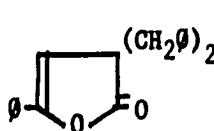
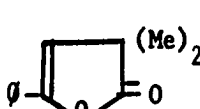
Studies on the Proof of Structure of (X)

In several cases both of the isomeric butenolides corresponding to (IX) and (X) have been isolated (16,25,33) but, in each case it has been possible to convert one of the isomers into the other more stable form. This isomerization does not occur with butenolides which contain exo-unsaturation or disubstituted α or β positions since the absence of an active hydrogen renders migration of the carbon-carbon double bond impossible. The accumulation of evidence to date indicates that butenolides with α or β substituents are more stable in the α, β -unsaturated form. Butenolides with γ substituents but without α or β substituents are known to be more stable in the β, γ -unsaturated form.

Several workers have prepared "triphenyl butenolide" (X) but at present no unequivocal proof of position of unsaturation has been reported for this compound. Crawford (2) proposed structure (IX) based on the formation of a keto acid when the butenolide was saponified. She argued that if the compound had structure (X), it would give a hydroxy unsaturated acid when saponified. This argument failed to take into account the isomerization that this hydroxy unsaturated acid or the intermediate anion can undergo. Linstead and co-workers (33) have shown that saponification of both isomeric butenolide pairs give the same keto acid. Putter and Dilthey (11) imply structure (X) based upon the butenolide's formation from benzoin phenylacetate by an aldol condensation with sodium amide. Yates and Stout (12) correlate the structures of several butenolides by infrared and ultraviolet studies and these support structure (X). Cross (34) reports the carbonyl absorption range for $\Delta^{\beta,\gamma}$ -butenolides to be 5.54-5.60 μ , and Bellamy (35) gives the range for $\Delta^{\alpha,\beta}$ -butenolides to be 5.68-5.75 μ . Examples of some compounds closely related to structures (IX) and (X) with their carbonyl absorption values are given in Table I. Waters (36) prepared (X) by reduction of γ -hydroxy- α,β,γ -triphenyl- $\Delta^{\alpha,\beta}$ -butenolide using stannous chloride and hydrochloric acid and assumed that the double bond did not migrate during the reduction. The previously reported (2) "difficult saponification of this compound was noted by Waters to be indicative of α,β -unsaturated butenolides, which are known to be more resistant to saponification than the corresponding β,γ -isomers. This information, in addition to the position of the carbonyl absorption, led Waters to reassign Crawford's structure (IX) as being actually

TABLE I

INFRARED CARBONYL ABSORPTION OF BUTENOLIDES

TYPE IX			TYPE X		
Compound	Microns	Ref.	Compound	Microns	Ref.
	5.59*	12		5.71* 5.73	12 This Work
	5.55	This Work		5.70* 5.66	12 This Work
	5.60*	This Work		5.70* 5.75	This Work
	5.60	This Work		5.68**	This Work
	5.58	This Work		5.71*	37
	5.55* 5.60	This Work		5.69* 5.73**	37 This Work
	5.55**	This Work		5.70*	37

Unmarked values in KBr

* in CHCl_3

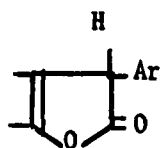
** neat

structure (X). This present author feels that part of this resistance to saponification is due to the low solubility of this and related heavily substituted butenolides in the aqueous ethanolic sodium hydroxide saponification mixture. Several α, α' -disubstituted- $\Delta^{B\gamma}$ -butenolides have been found to require a minimum saponification period of at least 12 hours with this reagent. In 95% ethanol, however, Crawford reported that saponification of her compound required only one hour.

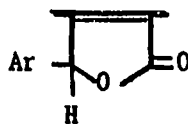
In this work several attempts were undertaken to more firmly elucidate the structure of this "triphenyl butenolide" based upon reactions designed to locate the double bond, including permanganate oxidation, ozonolysis, epoxidation and hydroboration procedures. The inconclusive results of these attempts may be summarized briefly. Permanganate oxidation gave only benzoic acid and recovered starting material. Ozonolysis followed by saponification of the reaction mixture gave benzoic acid and a small amount of uncharacterized hydroxy lactone. With perbenzoic acid at 0° for 2 days, 95% of the starting material was recovered. The use of 40% peracetic acid resulted in a recovery of 88% of the starting material. The procedure of Emmons and Pagano (38) using buffered peroxytrifluoroacetic acid on this material gave a 92% recovery of the starting material and 4% of a dimer of (X) as the only products isolable. In view of the difficulty of finding a reagent which would selectively attack the double bond, an in situ hydroboration was tried using sodium borohydride and boron trifluoride etherate in tetrahydrofuran. Although almost 75% of the starting material was recovered a small amount of an alcohol m.p. 171-172° was isolated by chromatography. This product had no carbonyl absorption in the infrared. However, due

to the very low yield of this alcohol complete identification was not possible. The small amount of sample available plus its limited solubility prevented interpretation of the NMR spectrum.

The failure to locate the position of the double bond by a chemical approach led to the examination of the butenolide using the nuclear magnetic resonance (NMR) technique. For a compound having only one nonaromatic hydrogen the NMR spectrum should be quite conclusive. The NMR spectrum of this compound had a peak at 3.78 τ (unsplit) which was assigned to the tertiary hydrogen. For strict correlation, reference spectra for the two systems (IXa) and (Xa) would be needed. How-



IXa



Xa

ever, at present, the available NMR values for these systems are limited. Some systems which are very close to the required cases are given in Table II.

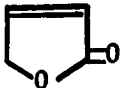
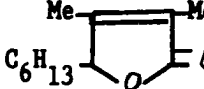
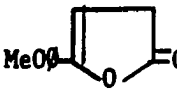
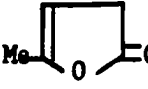
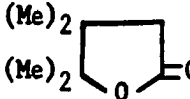
If the effects of conjugation due to the aromatic rings are of the same magnitude for both (IXa) and (Xa) types, then the observed value is in closest agreement for the structure (Xa). This is additional support for structure (X) for this compound, and this structure for triphenyl butenolide will be used throughout the rest of this thesis.

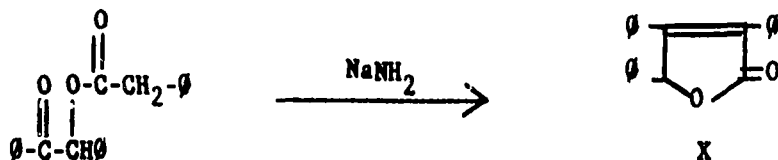
Preparation of α,β,γ -Triphenyl- $\triangle^{\alpha,\beta}$ -butenolide (X)

Putter and Dilthey's (11) method of preparation of (X) from benzoin phenylacetate employed solid sodium amide and gave a relatively low yield (22%), according to the equation below. The inconvenience of

TABLE II

NMR τ VALUES OF SELECTED SYSTEMS

System	Type IXa $\begin{array}{c} \text{O} \\ \\ -\text{C}=\text{C}-\text{C}-\text{C}- \\ \\ \text{H} \end{array}$	Type Xa $\begin{array}{c} \text{O} \\ \\ -\text{C}-\text{C}-\text{C}-\text{O}- \\ \\ \text{H} \end{array}$	Ref.
		5.08	39
		5.14	40
		4.73	This Work
		5.64	41
	7.60	5.63	39
$\text{>C}=\text{C}-\text{CH}_2-\text{OH}$		5.87	39
$\text{>C}=\text{C}-\text{CH}-\text{OH}$		5.89	39
$\text{>C}=\text{C}-\text{CH}_2-\text{OR}$		6.07	39
$\text{>CH}-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}$		4.99	42
	6.65		This Work
	6.95		This Work
	7.57		39
$\text{>CH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}$	7.52		42



this method led to a modification using the general procedure of Hauser (43), whereby, sodium amide is prepared in liquid ammonia and used as such or after replacement of the ammonia by ether. Other solvent and base combinations were studied in an attempt to raise the yield of the product. These results are summarized in Table III.

The effect liquid ammonia had on the condensation cannot be determined, but very erratic results were obtained when it was used. In some cases the yield of (X) dropped to as low as 12%, but the usual yield was in the range of 30-35%. When the ammonia was replaced with ether the yields were more reproducible in the range of 32-39%. The only other procedure found which showed any merit was the use of sodium hydride in tetrahydrofuran. The effectiveness of this reaction (44% yield of the product) was reduced due to formation of a hydroxy butenolide by-product (which is produced from (X) and will be discussed later) in 15% yield based on ester consumed. In most of these preparations some saponification of the benzoin phenylacetate, (up to 26% in some cases) prior to the condensation step, was also observed which reduced the overall yield of the product. In addition, some accidental saponification of (X) was also observed occasionally.

Separation of the lactone from the saponification products proved to be difficult. The acidic materials could be removed by extracting the crude reaction mixture with dilute base, but removal of

TABLE III

PREPARATIONS OF α, β, γ -TRIPHENYL- $\Delta^{\alpha, \beta}$ -BUTENOLIDE

Solvent	Base	Temp. C ^o	Time Hrs.	Yield %
NH ₃ -Et ₂ O	NaNH ₂	-40	4	30-60.5
THF	NaH	Reflux	3	44*
Et ₂ O	NaNH ₂	30	3	32-39
Benzene	NaH	Reflux	2.5	31
Benzene	NaOCH ₃	Reflux	3	14

*15% of a by-product derived from the lactone was also obtained

the remaining benzoin by recrystallization was attended by serious losses of the product. The best procedure for avoiding these losses was chromatography of the crude product on alumina. The lactone (X) was eluted as a yellow band (followed by the benzoin) which when recrystallized from methanol gave a very pure product.

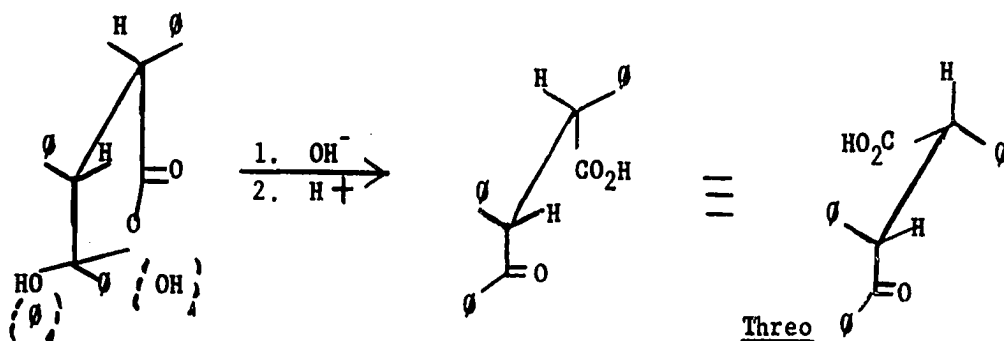
At this point, some observations pertinent to the nature of the keto acids resulting from the saponification of (X) should be noted.

Crawford (2) reported that the saponification of (X) forms two keto acids, one melting at 202° and the other at 212° . In a later paper (44) she prepared the corresponding substituted butyric acids m.p. 154° and 140° , respectively, from the keto acids by a Clemmensen reduction. Based on the intramolecular Friedel-Crafts ring closure of these respective butyric acids, to give the corresponding tetralone and indanone, Lednicer and Hauser (45) have tentatively assigned threo and erythro configurations to these butyric acids.

In this work the intentional saponification of (X) was found to give only the low melting threo keto acid. The acid obtained from the accidental saponification of (X), mentioned above, was also found to consist only of the low melting form. In two cases preparations of (X) gave an acidic material, obtained by extracting the reaction mixture with base, which had m.p. $228-229^{\circ}$ and must be different from the two keto acids that Crawford (2) prepared. The infrared spectrum of this new acid showed single hydroxyl and only one carbonyl absorption, indicating that it had the pseudo acid form. A molecular weight value of 332, and the elemental analysis indicated the expected formula of $C_{22}H_{18}O_3$. When a sample of this new acid was dissolved in hot alcoholic

sodium hydroxide and precipitated with acid only the low melting keto acid was obtained. The infrared spectrum of this crude acid indicated that the pseudo form had been completely converted into the keto form. At no time during the course of this work, however, has the low melting keto acid been observed to revert to the pseudo form.

This evidence indicates that this pseudo acid is the cyclic form of Crawford's (2) 202⁰ acid. Since this keto acid had been assigned the threo configuration, this pseudo acid must also preserve this threo arrangement about the α and β positions. The configuration about the new asymmetric carbon at the γ position is not known, but the γ -phenyl group would be expected to be trans to the β -phenyl group. These structural relationships are summarized in the scheme below.



Preparation of α -Benzyl- α,β,γ -triphenyl- $\Delta^{\beta,\gamma}$ -butenolide (XV)

Several different procedures were employed to prepare this compound, the results of which are summarized in Table IV (reactions 1-6).

The use of benzyl benzenesulfonate as the alkylating agent was found to give the highest yield of (XV) (Fig. 1), which can be attributed entirely to the benzenesulfonate function being a better leaving group than chlorine. The reactions using aromatic solvents and insoluble bases require heating to initiate any appreciable reaction and the

FLOW SHEET FOR REACTIONS OF (X)

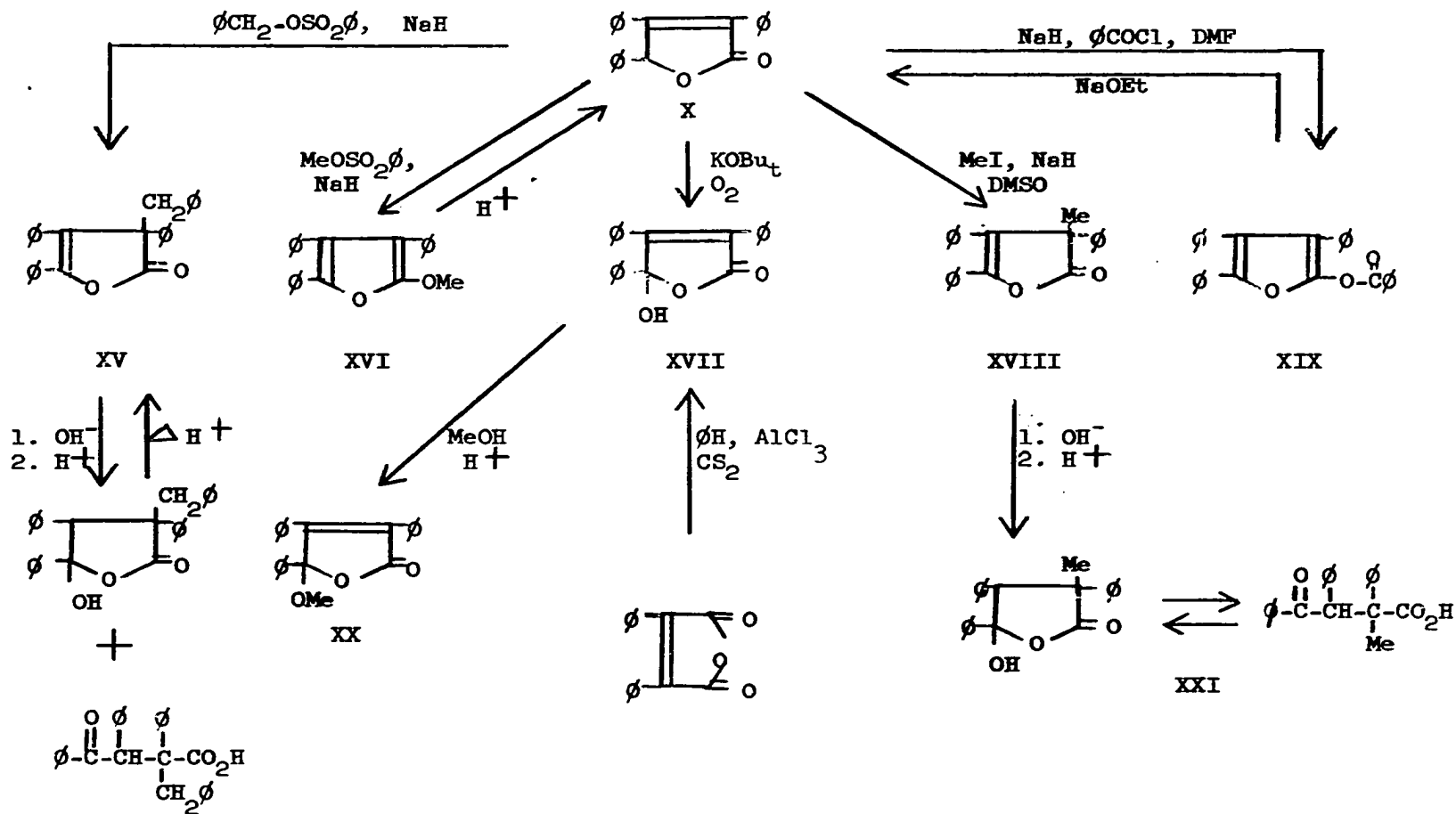


TABLE IV

 ALKYLATIONS OF α, β, γ -TRIPHENYL- $\Delta^{\alpha, \beta}$ -BUTENOLIDE

	Alkylating Agent	Base	Solvent	Temp. C ^d	Time hrs.	Yield %
1.	$\text{OCH}_2\text{OSO}_2\text{O}$	NaH	Toluene	75 ^a	0.75 ^a	75 (XV)
2.	OCH_2Cl	NaH	Toluene	Reflux	13 ^a	56 (XV)
3.	OCH_2Cl	NaOMe	Toluene	Reflux	4.5	36 (XV)
4.	OCH_2Cl	NaH	Benzene	Reflux	4.5	26 (XV)
5.	OCH_2Cl	LiBu _n	Benzene	Room	0.25 ^a	8 (XV)
6.	OCH_2Cl	KOBu _t	Et ₂ O	Room	4.25	38 ^b (XVII)
7.	MeOSO_2O	NaH	Toluene	Reflux	3	21 ^c (XVI)
8.	MeI	NaH	DMSO-OH (2.5:1)	Room	2.75	84 (XVIII)
9.	MeI	NaH	DMSO-OH (1:2.4)	Room	2	8 ^b (XVIII)
10.	$\text{Cl}_3\text{CCO}_2\text{Me}$	NaH	DMSO-OH (5:1)	Room	1.33	74 ^d
11.	OCOC1^e	NaH	DMF-OH (2:1)	Room	0.75	44 ^b (XIX)
12.	OCOC1^e	NaH	Toluene	Reflux	2	5 ^b (XIX)

a after formation of anion (XI)

b unreacted (X) also recovered

c O-alkylation

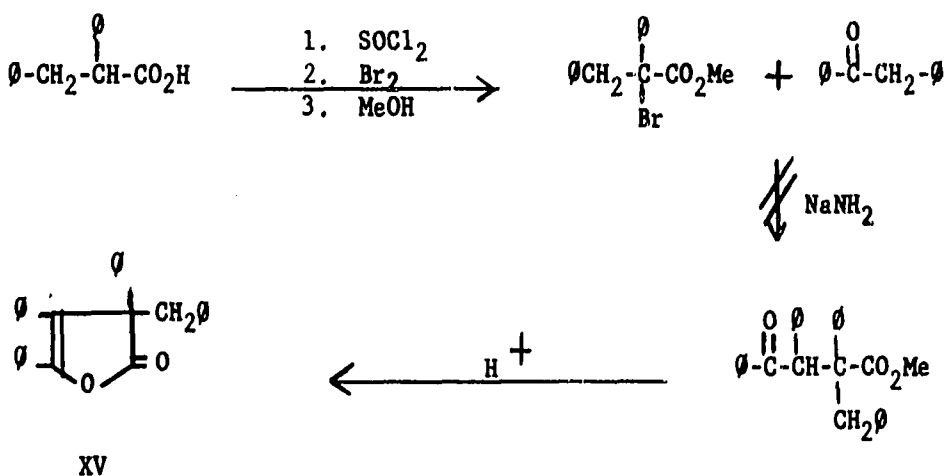
d dimer of (X)

e acylating agent

higher boiling toluene gives the best yield under these conditions. However, the instability of benzyl benzenesulfonate, requires that before the sulfonate is added, the reaction mixture must be cooled after formation of the anion (XI). For this reason the preparation and use of the sulfonate is inconvenient. The comments of Kochi and Hammond (46) on the instability of the benzyl tosylates are also applicable to the benzenesulfonate. A purified sample of this compound, while stable at -80° for several months, was observed to decompose at room temperature within 5 hours to a dark colored plastic mass which after standing for one month had lost most of the color. The nature of this plastic mass was reviewed by Kochi and Hammond which indicates that it is a polybenzyl polymer.

After this series of reactions was completed a better procedure for these alkylations was developed, which is described in detail later, which employed dimethyl sulfoxide (DMSO) as the solvent permitting milder conditions and resulting in higher yields of products. This new procedure, however, was not applied to triphenyl butenolide.

An attempted proof of structure for (XV) using the following synthetic sequence failed at the condensation step.



Degradative approaches to the structure of (XV) encountered the same lack of reaction already mentioned for similar reactions on (X). For example an attempted epoxidation of (XV) using 40% peracetic acid in acetic acid for 15 hours failed; only starting material was recovered. Perbenzoic acid at 0° for 6 days resulted in a recovery of 93% of the starting material and a residue of 0.05 g. which when examined by infrared absorption was found to consist of approximately 10% of the starting material and no more than 0.02 g. (6.5%) of an epoxide with absorption at 7.92μ (epoxides $7.94-8.07\mu$) (34). However, due to the low conversion to the epoxide these reactions were not examined further.

While no direct proof of structure of (XV) was obtained, the infrared spectrum showed carbonyl absorption at 5.60μ , consistent with the absorption of other $\Delta^{\beta,\gamma}$ -butenolides.

In addition, saponification of (XV) was found to give a quantitative yield of two acids in a ratio of 2.5:1. Infrared absorption spectra indicated that the acid formed in greater amount (m.p. $177-178^{\circ}$) was a pseudo acid, which did not give an acceptable neutralization equivalent; the acid formed in lesser amount was a keto acid (m.p. $224-225^{\circ}$ dec.) and gave a neutralization equivalent of 420 (expected molecular weight 421). A mixture of these acids could be relactonized, using the procedure of Crawford (2), with 65% sulfuric acid to give (XV) in 17% yield.

Both the infrared spectra of (XV) and the relactonization of the keto acid are indicative of an α -benzyl.

Preparation of 2-Methoxy-3,4,5-triphenylfuran (XVI)

In contrast to benzyl benzenesulfonate which was found to give

C-alkylation in good yield, methyl benzenesulfonate was found to give O-alkylation, although in low yield.

Reaction of (X) with sodium hydride and methyl benzenesulfonate in refluxing toluene gave a 21% yield of (XVI) - see Table IV reaction 7. Attempted chromatography of (XVI) on alumina resulted in its hydrolysis to (X). The Lewis acid nature of alumina is known to promote hydrolysis of acid sensitive compounds. On intentional acid hydrolysis this furan is converted into (X) in good yield.

Pierce and Joulie (47) have reported that methyl trichloroacetate gives a preferred O-alkylation. When this procedure was tried with (X) only a dimer of (X) was obtained in yields of 57 and 74%, with no evidence of the furan being formed (see Table IV reaction 10).

Preparation and Proof of Structure of γ -Hydroxy- α,β,γ -
triphenyl- $\Delta^{\alpha,\beta}$ -butenolide (XVII)

In preparations of (X), it was discovered that in almost every reaction run at or near room temperature, an acidic material (XVII) formed in yields of 0.2-15%. And in reactions where (X) was used as starting material, (XVII) was formed in yields of 5-45.5%. For example, the highest yield of this by-product (45.5%) was the result of an attempted Grignard reaction using phenylmagnesium bromide with (X) in THF at reflux for 3 hours. This reaction gave in addition a dimer of (X) in 21% yield.

These reactions had all been run without special precautions to exclude oxygen. To establish that oxygen was reacting with anion (XI), oxygen was bubbled through an ether solution of (X) and potassium t-butoxide. This reaction gave crude (XVII) in 65% yield.

The acid (XVII) was readily soluble in dilute base, and gave a neutralization equivalent of 332. The infrared spectrum of XVII suggested a pseudo acid. The expected formula of $C_{22}H_{16}O_3$ was confirmed by analysis.

The structure of this acid was established by independent synthesis which consisted of a Friedel-Crafts reaction between diphenylmaleic anhydride and benzene, giving a 52% yield of acid (XVII) based on recovered starting anhydride (46% conversion). The two samples had identical infrared spectra and the mixed melting point was not depressed. Lutz and co-workers (8) have shown that it is not uncommon for γ -keto acrylic acids to exist in the cis pseudo acid form, which corresponds to the γ -hydroxy butenolide structure.

The pseudo ester (XX) was obtained by esterification of (XVII), using methanol and sulfuric acid, in 71.5% yield based on recovered unreacted acid (44% conversion). This pseudo ester and a sample of the compound supplied by Dr. H. H. Wasserman of Yale University, had identical infrared spectra and the mixed melting point was not depressed.

The proof of structure of (XVII) was completed before knowledge of the prior preparation of the pseudo ester (XX) by Wasserman was obtained. This compound was mentioned in a table in a paper by Yates and Stout (12). Waters (36), with Wasserman, had used essentially the same approach as employed in this work to prepare the acid (XVII) except that he did not use carbon disulfide as a cosolvent. Waters reported that some reaction occurs within 30 minutes in benzene at room temperature, whereas, in ethylene chloride at room temperature no reaction occurs during this same period, and at reflux only decomposition of

diphenylmaleic anhydride was observed. It is interesting to note that the reaction mixture in carbon disulfide had a dark red color, whereas, Waters described the reaction mixture in benzene as giving a green color.

Waters (36) obtained only a 42% yield of the pseudo acid which he found hard to purify and mentioned that the slightly impure product exhibits triboluminescence. While the procedure described in this work gave only a slightly better yield, none of the impure product from any of the reactions giving this compound was observed to exhibit triboluminescence; however, it did show a strong yellow-white fluorescence.

Waters (36) also mentioned a reaction between diphenylcadmium and diphenylmaleic anhydride which gave a quantitative crude yield of the pseudo acid (XVII) and which is therefore a better preparative method than the Friedel-Crafts procedure.

He also prepared the pseudo methyl ester (XX) in 91% crude yield using anhydrous methanol and anhydrous hydrogen chloride. In addition, he prepared the corresponding trans acrylic acid by irradiation of the pseudo acid (XVII).

Preparation of α -Methyl- α,β,δ -triphenyl- $\Delta^{\beta\delta}$ -butenolide (XVIII)

The following alkylation procedure was not developed until most of the previously described reactions had already been completed.

The methylation of (X) using methyl iodide and sodium hydride in dry DMSO and benzene at room temperature was found to be a faster and more convenient reaction than similar reactions using hydrocarbon solvents (in most cases the major part of the reaction in DMSO was complete within 30 minutes). The methyl iodide was observed to reflux

when solid (X) was added, although, no indication of warming of the reaction mixture was evident. The product (XVIII) was obtained in 84% yield (Table IV, reaction 8). Reversing the ratio of DMSO and benzene (Table IV, reaction 9) reduced the yield of (XVIII) to 15% based on recovered starting material (8% conversion). In this latter reaction the product and unreacted starting material were hard to separate even by chromatography on alumina.

In this latter case (reaction 9), the excess benzene was used to dissolve (X); as this solution was added to the DMSO-sodium hydride-methyl iodide mixture the initial evolution of hydrogen was observed to slow down. Apparently, although more (X) was present with each new addition, the increasing amount of benzene was at the same time retarding the reaction. Although, the reaction appeared to be over after 2 hours, unreacted (X) was still present. Excess benzene apparently tends to convert this reaction into the usual sluggish reaction as observed previously for hydrocarbon solvents.

For some recent reactions which DMSO can undergo with sodium hydride or methyl iodide (which may be involved to a slight extent under the reaction conditions cited above) see ref. (48,49).

Saponification of (XVIII) gave a good yield of the pseudo acid (XXI) which failed to form a dinitrophenylhydrazone derivative with Shine's reagent (50). It did not give an acceptable neutralization equivalent. The neutralization determinations were run in ethanol to insure solubility of the acid and the solution was boiled near the end point to expel carbon dioxide. The corresponding keto acid, which is also obtained, does give an acceptable neutralization equivalent. This

procedure was found to work satisfactorily with other pseudo acids but not with the very similar acid, γ -hydroxy- α -benzyl- α,β,γ -triphenyl-butanolide which has already been mentioned.

In summation, these alkylation reactions gave primarily the α -derivative and in one case the O-alkyl derivative, and, although they could theoretically also give the γ -derivative, at no time were any γ -alkyl products isolated. The only indication of any attack at the γ -position has been the isolation of the γ -hydroxy derivative (XVII) and the formation in some cases of a small amount of a dimer of (X) for which present evidence indicates a γ -linkage. The nature of this dimer will be described more fully later.

Acylation Reactions on α,β,γ -Triphenyl- $\Delta^{\alpha,\beta}$ -butenolide (X)

Although the alkylation reactions of (X) were found to give stable products in reasonable yields, attempted benzoylation of (X) was not as clear cut. In view of the preferred alkylations at the α carbon it was anticipated that acylation would also be confined to the α position. The α -benzoyl derivative is apparently known from the work of Yates and Stout (12), who reevaluated the earlier work of Putter and Dilthey (11) on the oxidation of tetracyclone. Putter and Dilthey had reported the failure of a benzoylation of (X) in an attempt to prepare this compound by an independent route. Yates and Stout report that their compound is sensitive to acids and bases and gives (X) upon cleavage.

Results of the reactions of (X) with benzoyl chloride are given in Table IV, reactions 11 and 12. It was found that the benzoyl chloride had to be free of hydrogen chloride before appreciable reaction

would occur. The reaction in DMF (no. 11) was found to give the highest yield of product (which is described later) although an equal amount of unreacted starting butenolide was also recovered. A competitive reaction of benzoyl chloride with DMF (51) apparently accounts for the incomplete reaction with (X). It was also observed that the reaction of DMF with benzoyl chloride in the presence of sodium hydride liberated hydrogen immediately at room temperature. In contrast, Coppinger (51) found that a mixture of benzoyl chloride and DMF had to be heated to 150° before the evolution of gas, in this case hydrogen chloride, started.

The reaction in toluene (no. 12), indicated that anion (XI) had not reacted to a very large extent under the conditions cited, since (X) was recovered in 74% yield. It is to be noted that when toluene or other hydrocarbon solvents are used as a reaction solvent, much longer reaction periods (than that used in no. 12) are needed for the highest yield of product to be obtained.

The product obtained in these two reactions was not the α -benzoyl butenolide of Yates and Stout (12), since it had a m.p. 199-199.5°. The material of Yates and Stout had a m.p. 110.5-112° with carbonyl absorption in the infrared at 5.59 and 5.96 μ . This product had carbonyl absorption in the infrared only at 5.70 μ which is not consistent with $\beta\gamma$ -unsaturated butenolides, but rather (incorrectly) indicates an α,β -unsaturated butenolide. However, two carbonyl absorption peaks would be expected for γ -benzoyl- α,β,γ -triphenyl- $\Delta^{\alpha,\beta}$ -butenolide (XII) (R-Benzoyl) but structure (XIX, fig. 1) can account for the single carbonyl absorption more easily since the counteracting effects of aryl ester absorption (5.78-5.83 μ) and vinyl

ester absorption (5.56-5.65 μ) might be expected to show a modified absorption somewhere near 5.70 μ . A satisfactory elemental analysis could not be obtained in spite of the sharp melting point and the fact that several recrystallizations did not change this range. A molecular weight determination gave a value of 421 which is consistent with structure (XIX).

Saponification of this product was found to give threo α,β -diphenyl- β -benzoylpropionic acid, obtained also by the previously described saponification of (X), in quantitative yield along with benzoic acid. This indicates reversal of the condensation under the saponification conditions.

Transesterification of this product with ethanol and sodium ethoxide gave a definite odor of ethyl benzoate (indicated also by matching characteristic infrared absorption peaks with authentic ethyl benzoate). The crude reaction mixture after removing some starting material (10%) by recrystallization from ethanol and removing most of the ethyl benzoate in vacuo, gave when recrystallized from methanol $\alpha,\beta\delta$ -triphenyl- $\Delta^{\alpha,\beta}$ -butenolide, which was identical to authentic (X). This reaction indicates the reversibility of the condensation and also that the butenolide was still intact.

The NMR spectrum of this benzoyl derivative had absorption at 1.85 τ (weak doublet) which was assigned to the two ortho hydrogens of the benzoate group. Present evidence (39) indicates that the ortho hydrogens of benzoic acids absorb close to 1.88 τ . In this work the esters methyl benzoate, ethyl benzoate, benzyl benzoate and phenyl benzoate also were found to have absorption for the ortho hydrogens

within the range 1.88-1.97 τ . On the other hand aromatic ketones and aldehydes (39) had absorption for the ortho hydrogens within the range 2.03-2.65 τ . On the basis of the NMR and infrared results, the γ -acyl butenolide (XII) (R-Benzoyl) can now be eliminated from consideration and structure (XIX) assigned to this O-benzoyl derivative.

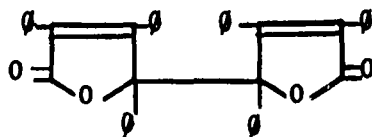
Oxidative Dimers of (X)

In several cases a high melting material has been isolated from various reactions of (X). Preliminary studies, limited by the small amounts available, indicate that it is of a dimeric nature.

For example a very low yield (approx. 1%) of material m.p. 230-232.5° dec. and molecular weight 605 was obtained from a preparation of (X). An attempted Grignard reaction on (X) gave a 21% crude yield of material which when purified had m.p. 205-207° dec. and whose IR and NMR curves were identical with the above material. These two products are probably stereoisomers of each other. An attempted epoxidation of (X) using trifluoroperacetic acid gave a 4% yield of product having m.p. 202-204° dec. (identical by IR to the 207° dec. material above but slightly impure). The highest yields of this substance (74 and 57% crude) were obtained from attempted O-alkylation of (X) using methyl trichloroacetate. A sample from these reactions (recrystallized but still impure) had a m.p. 199° dec. (highest upper limit observed) and a molecular weight value of 713.

The NMR curves indicated only aromatic hydrogens and absence of the aliphatic tertiary hydrogen (3.78 τ) present in (X). The infrared spectre from all of these preparations were identical and indicate the $\Delta^{\alpha,\beta}$ -butenolide form, based on the carbonyl absorption at 5.68 μ .

Waters (36) prepared a bis lactone from (X) using sodium and iodine to give a product m.p. 185-200° which was formulated as,



although the carbon analysis of the compound was low by 0.89%. He reports carbonyl absorption for his compound at 5.65 μ . It is very likely that his bis lactone and the dimers described above are identical, since these spectra and his published spectrum bear a close resemblance.

A more complete discussion on the problem of similar dimers will be given in Part II.

Hydrogenations of α, β, γ -Triphenyl- $\Delta^{\alpha, \beta}$ -butenolide (X)

Hydrogenation and hydrogenolysis of (X) in ethyl acetate using 10% Pd/C at 25° and 44.5 p.s.i. for 23 hours gave an 84% yield of triphenylbutyric acid. Since hydrogenation ordinarily proceeds with *cis* addition, this acid therefore has the erythro configuration. This lends definite support for Lednicer and Hauser's (45) previous assignment for this acid.

In this connection, further support for the correlation of Lednicer and Hauser's assignments with the work of Crawford (2) was obtained by Kelly (52). Kelly found that the hydrogenation (which is discussed later) of the pseudo acid (XVII) gave the 212° keto acid of Crawford; again addition of hydrogen in the cis manner indicates that this keto acid has the erythro configuration. Thus the configurations assigned by Lednicer and Hauser to the α, β, γ -triphenylbutyric acids,

and by extension to the corresponding γ -keto acids of Crawford may now be considered to be firmly established.

The strange behavior of the erythro triphenylbutyric acid prepared above when recrystallized from alcohol and then from benzene is interesting. The analytical sample of this acid was obtained from benzene and had m.p. 144-145^o. When a sample of this acid was recrystallized from ethanol and air dried for 6 hours the sample gave off bubbles when heated at 120^o, and then melted at 140-148^o. This same sample after standing in air for 3 days then showed no gas evolution at 120^o and melted at 149.5-151^o. If this material were then recrystallized from benzene, the melting point was 145-146^o and it showed an infrared spectrum identical to that of the original acid.

Crawford, Davidson and Plunkett (44) stated that their (erythro) triphenylbutyric acid m.p. 139-140^o was an ethanol solvate. Their melting point corresponds to the 145^o material obtained in this work, (from benzene) which is not a solvate.

Lednicer and Hauser (45) did not state that their erythro acid is a solvate even though it was recrystallized from alcohol. Lednicer (53) felt that his erythro acid may have been a solvate but also suggested that Crawford's 158^o, solvent free "erythro" form (44) might actually be the more stable threo form resulting from isomerization.

It is not likely that the variable melting point behavior, described above in this work, is due to isomerization, since the original melting point was confirmed in the end and also because these recrystallizations resulted in only a minor loss of material overall (not the result of isolating unisomerized acid). While the existence of a solvate

for this erythro acid may have been indicated by the ethanol recrystallization, the results strongly indicate that polymorphism may be responsible for this change in melting point with change in solvent.

The esterification of erythro triphenylbutyric acid, obtained in the hydrogenation above, using methanol and sulfuric acid gave the methyl ester m.p. 164-164.5° which corresponds to the methyl ester (m.p. 159-160°) obtained by Crawford (44) from the "alcoholate". This reaction indicates that Crawford's alcoholate and the acid obtained in this work, which is not a solvate, are identical and that this methyl ester can now be assigned the erythro configuration.

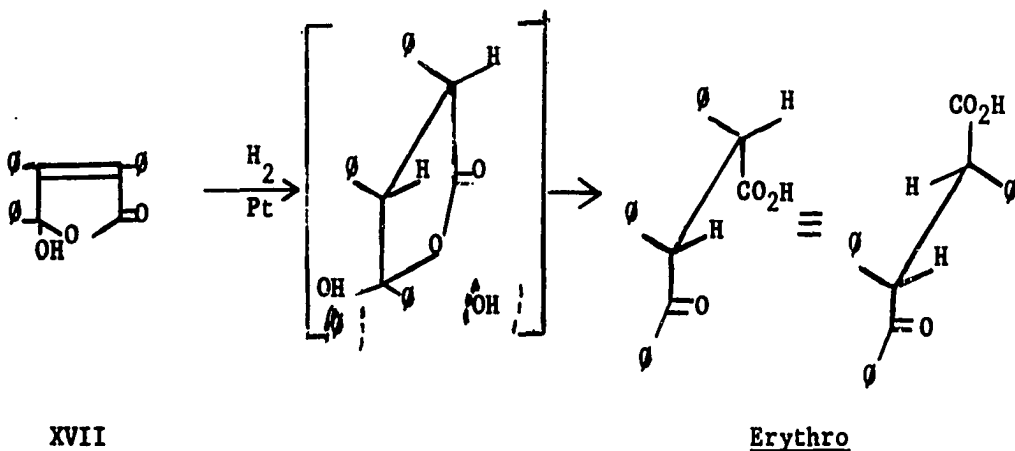
Hydrogenation of (X) in ethyl acetate using 5% Pt/C at 25° and atmospheric pressure for 5.3 hours resulted in a 79% yield of α, β, γ - triphenylbutanolide and a 3.5% yield of erythro α, β, γ - triphenylbutyric acid.

Hydrogenation of (X) with Adams catalyst instead of Pt/C gave entirely different results. The reaction was interrupted after 26 hours, although hydrogen absorption had not stopped (5 equiv. consumed). The neutral material had carbonyl absorption at 5.75 μ and very strong carbon-hydrogen stretching vibrations at 3.46 and 3.55 μ indicating that reduction of the aromatic rings had occurred. The molecular weight and elemental analysis indicated that 2 of the benzene rings had been reduced in addition to reduction of the α, β -double bond. This product was isolated in 29.5% yield. The acidic fraction gave erythro α, β, γ - triphenylbutyric acid in 39.5% yield, and the threo acid in 15% yield.

Hydrogenations of γ -Hydroxy- α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide (XVII)

Hydrogenation of the pseudo acid (XVII), in ethyl acetate for

4 hours at atmospheric pressure using Adams catalyst, gave γ -hydroxy- α,β,γ -triphenylbutyric acid in 64% yield which melts with loss of water to form α,β,γ -triphenylbutanolide. Kelly (52) used the same conditions as above, but stopped the reaction after the absorption of one equivalent of hydrogen to give a 95% yield of Crawford's (2) higher melting (212°) α,β -diphenyl- β -benzoylpropionic acid. Since hydrogenation ordinarily proceeds with cis addition, this result provides further support for the assignment of the erythro configuration to this acid. These structural relationships are summarized in the scheme below.



Hydrogenation of α -Benzyl- α,β,γ -triphenyl- $\Delta^{2,3,4}$ -butenolide (XV)

The hydrogenation of this compound with Pd/C under the same conditions as described for (X) gave a mixture of acids in quantitative crude yield, which could be partially separated by recrystallization to give a low melting form m.p. $104-105^\circ$ and a high melting form m.p. $166.5-172^\circ$ in a ratio of approximately 6:1. Four successive recrystallizations of the low melting form from benzene-hexane resulted in a slowly increasing melting range (the melting point of the material from the last recrystallization was $111-123^\circ$). From the mother liquors of these

recrystallizations the higher melting form m.p. 151-169° was obtained. Due to the difficulty in obtaining any pure compounds from this hydrogenation no further reactions were attempted.

PART I

EXPERIMENTAL

All melting points and boiling points are uncorrected. The reaction solvents ether, tetrahydrofuran, benzene and toluene were dried over sodium wire. Dimethyl sulfoxide was dried over calcium hydride for six days at 100° and distilled from calcium hydride under reduced pressure (b.p. 84-84.5° at 18 mm.). Dimethylformamide was dried with calcium hydride followed by passage through a column of 4A molecular sieve (Linde). Commercial sodium hydride was powdered under a nitrogen atmosphere in a dry box. The term "worked up in the usual way", unless otherwise described, for a basic aqueous phase means that the solution was acidified with hydrochloric acid, extracted several times with benzene, the combined benzene extracts washed with water, the benzene solution dried over sodium sulfate, and the solution concentrated. Molecular weight determinations were performed in benzene using a Mechrolab vapor pressure osmometer. Infrared spectra were recorded by a Perkin-Elmer Model 21 spectrophotometer and nuclear magnetic resonance spectra by a Varian A-60 spectrometer.

Benzoin Phenylacetate. This compound was prepared by a modification of the method of Putter and Dilthey (11). Phenylacetic acid (50 g., 0.37 mole) and excess thionyl chloride (80 g.) were refluxed for 75 minutes on a steam bath until evolution of gases ceased. The excess

thionyl chloride was removed by distillation under reduced pressure. The last traces of thionyl chloride were removed by distillation with benzene under reduced pressure. Benzoin (77 g., 0.36 mole) was added to the acid chloride and the mixture was heated 2 hours on a steam bath until the evolution of hydrogen chloride stopped. Dry ether (140 ml.) was added and the solution was cooled in the refrigerator. There was obtained 95 g. (79%) of ester, m.p. 70-71°. Recrystallization from methanol gave 91 g. of large colorless crystals, m.p. 71-72° (lit. (11) 71°).

α,β,γ -Triphenyl- $\Delta^{\alpha,\beta}$ -butenolide (X). A modification of the method of Putter and Dilthey (11) was used. Sodium amide (0.034 mole) was prepared, using the method of Hauser (43), in 500 ml. of liquid ammonia and stirred while a solution of benzoin phenylacetate (10 g., 0.03 mole) in 300 ml. of dry ether was added dropwise over approximately a 30 minute period. Stirring was continued for an additional hour. The excess ammonia was removed on a steam bath. Cold water (100 ml.) was added to destroy the excess sodium amide, followed by 5 ml. of cold acetic acid. The ether phase was washed with water, dried over sodium sulfate, evaporated to dryness and the residue recrystallized from methanol. There was obtained 5.7 g. (60.5%) of product, m.p. 122.5-125°. Recrystallization from methanol raised the melting point to 125-126° (lit. (11) 125°).

In some reactions the methanol recrystallization did not give a pure product; such material typically melted over the range 109-121°. In these cases the crude product was chromatographed on alumina using benzene as eluant. The first yellow band to come off the column

consisted of the lactone. The recovery of pure product (X), (typical m.p. 125.5-126°) after methanol recrystallization, was approximately 50%. The second yellow band to come off the column consisted of benzoin.

Reactions in which the liquid ammonia was replaced with ether after the formation of the sodium amide resulted in the formation of a large amount of an ether insoluble green colored sludge. Also, the yields were not as high as when liquid ammonia was the principal solvent. This sludge, which is difficult to filter, could be kept to a minimum by using no more than a 5% excess of sodium amide.

An alternate preparative method consisted of adding the ester in several portions to a refluxing mixture of tetrahydrofuran and a 5% excess of sodium hydride. The vigorous evolution of hydrogen became more moderate as each additional portion of ester was added, and the initial lemon yellow color changed to dark green. The solvent was removed under reduced pressure and the residue was taken up in benzene and extracted with water. The product was obtained from methanol. For additional experimental conditions for this reaction see Table III.

α -Benzyl- α,β,γ -Triphenyl- $\triangle\beta,\gamma$ -butenolide (XV). From Benzyl Benzenesulfonate. To a stirred refluxing suspension of sodium hydride (0.5 g., 0.021 mole) in 150 ml. of dry toluene was added 3.12 g. (0.01 mole) of solid (X), and the resulting red solution was refluxed for 2 hours until hydrogen evolution stopped. The reaction mixture was then cooled to 75° and 2.48 g. (0.01 mole) of recrystallized benzyl benzenesulfonate (54), m.p. 61-61.5° (lit. (55) m.p. 60°), was added. The red color changed to yellow immediately, and slowly faded to a buff

color after 45 minutes. The mixture was filtered, extracted with water, dried over sodium sulfate, and evaporated to dryness. The residue was recrystallized from methanol to give 2.12 g. of product, m.p. 152-154°. Concentration gave an additional 0.75 g. (m.p. 149-152.5°) and 0.15 g. of less pure product. The total crude yield was 75%. Recrystallization of the first crop from methanol gave 2.01 g. of product m.p. 154-155°.

The aqueous phase was worked up in the usual way to give 0.17 g. (5%) of the acidic γ -hydroxy- α,β,γ -triphenyl- $\Delta^{\alpha,\beta}$ -butenolide (XVII) m.p. 176-177°. A mixed melting point with the analytical sample described later was not depressed.

From Benzyl Chloride. To a stirred refluxing suspension of sodium hydride (1.54 g., 0.064 mole) in 300 ml. of dry toluene was added 10 g. (0.032 mole) of (X), dissolved in 250 ml. of toluene. The solution was refluxed for 1.5 hours. A solution of 4.05 g. (0.032 mole) of benzyl chloride in 50 ml. of toluene was added over a 0.5 hour period, and refluxing was continued for an additional 13 hours. The reaction mixture was cooled, filtered, extracted with water, dried over sodium sulfate, and concentrated. There was obtained 7.15 g. (56%) of product, m.p. 148-150.5°. Recrystallization from toluene gave 5.16 g. (40%) of colorless crystals, m.p. 151-152°; infrared absorption (CHCl_3) 5.60μ .

Anal. Calcd. for $\text{C}_{29}\text{H}_{22}\text{O}_2$: C, 86.54; H, 5.51.

Found: C, 86.37; H, 5.62.

2-Methoxy-3,4,5,-Triphenylfuran (XVI). To a stirred refluxing suspension of sodium hydride (0.5 g., 0.021 mole) in 70 ml. of toluene was added a solution of (X) (3.12 g., 0.01 mole) and methyl

benzenesulfonate (56) (1.72 g., 0.01 mole) in 30 ml. of toluene over a 15 minute period. Hydrogen evolution had stopped after one hour, but the mixture was refluxed for an additional 2 hours. The reaction mixture was cooled, filtered, washed with water, dried over sodium sulfate, and concentrated. Addition of hexane to the hot concentrated solution gave on cooling 0.67 g. (21%) of the ether (XVI), m.p. 165-166.5°. Two recrystallizations from benzene-hexane gave an analytical sample, m.p. 166-166.5°. Carbonyl absorption in the infrared was absent.

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.64; H, 5.65; $-OCH_3$, 9.51.

Found: C, 84.71; H, 5.67; $-OCH_3$, 9.35.

Another identical reaction which gave a mixture of the furan and starting material was recrystallized to remove most of the lactone. Attempted chromatography of the furan residue on alumina resulted in isolation only of butenolide (X).

γ -Hydroxy- α,β,γ -triphenyl- $\Delta^{\alpha,\beta}$ -butenolide (XVII). By

Oxidation. Into a 500 ml. round bottom flask, equipped with a condenser and sintered glass bubbler was placed 0.5 g. (0.0016 mole) of (X), 0.2 g. (0.0018 mole) of commercial potassium t-butoxide, and 200 ml. of dry ether. An orange color formed immediately. The solution was stirred magnetically while oxygen was bubbled in slowly for 4 hours. The color faded to a light yellow. The ether solution was extracted with dilute sodium sulfite followed by water. The acidic product was isolated from both the ether (0.27 g., m.p. 168-176°) and aqueous (0.07 g., m.p. 143-164°) phases using the previously described work up procedures. The total crude yield was 0.34 g. or 65%. A sample recrystallized from methanol had m.p. 175-176°. An analytical sample from a

previous reaction was obtained by recrystallization from benzene and had m.p. 177.5-178°; infrared absorption (KBr) 3.10 and 5.75 μ .

Anal. Calcd. for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91; mol. wt., 328.

Found: C, 80.32; H, 4.96; new. eq., 332.

By Independent Synthesis. This procedure was modeled after that of Lutz (8). To a magnetically stirred mixture of aluminum chloride (1.33 g., 0.01 mple), 9 ml. (0.1 mole) of benzene and 20 ml. of carbon disulfide at reflux was added dephenylmaleic anhydride (57) (prepared by dehydrogenation of 2,3-diphenylsuccinic acid (58) obtained from hydrolysis of the nitrile (59)) (1.2 g., 0.0048 mole) in small portions over a 15 minute period. The dark red mixture was stirred at reflux for an additional 30 minutes then stirred overnight at room temperature. The reaction mixture was poured onto a crushed ice and hydrochloric acid mixture. The phases were separated and the aqueous phase was extracted with three portions (20 ml.) of benzene. The benzene solutions were combined with the original organic fraction, and the combined organic phases were extracted with dilute sodium carbonate. The organic phase afforded 0.13 g. of recovered diphenylmaleic anhydride m.p. 153.5-160.5° (pure starting anhydride had m.p. 159.5-160.5°)

The aqueous phase was clarified with Norite and worked up as usual. There was obtained 0.68 g. of the product, m.p. 177-178°. A mixed melting point with the analytical sample described above was not depressed and the infrared spectra were identical. Further concentration gave an additional 0.05 g. of the product, m.p. 173-176°. The total crude yield based on recovered anhydride was 52% (46% conversion.

γ -Methoxy- α,β,γ -triphenyl- $\Delta^{\alpha,\beta}$ -butenolide (XX). Into a

50 ml. Erlenmeyer flask, equipped with a condenser was placed the pseudo acid (XVII) (0.5 g., 0.0015 mole), 10 ml. of anhydrous methanol and 2 drops of concentrated sulfuric acid. The solution was refluxed for 15.5 hours. Saturated sodium acetate (1 ml.) was added to neutralize the acid and the excess methanol was evaporated by an air stream. Water was added and the mixture was extracted with benzene, the organic phase was washed with dilute sodium hydroxide, water, dried over sodium sulfate, and evaporated to dryness. There was obtained 0.35 g. (67%) of crude oily pseudo ester which was chromatographed on alumina using benzene as eluant. Concentration of the main fraction and diluting the hot solution with hexane gave on cooling 0.16 g. of the ester, m.p. 110-111^o; a second crop of 0.07 g. of product m.p. 108-109^o was obtained by concentrating the solution.

Work up of the aqueous phase gave 0.19 g. of pure starting material. The yield of recrystallized product allowing for recovered starting material was 71.5% (44% conversion).

An analytical sample of the pseudo ester from benzene-hexane had m.p. 110.5-111^o; the infrared spectrum showed a single carbonyl absorption at 5.66 μ (KBr).

Anal. Calcd. for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30; $-OCH_3$, 9.06.

Found: C, 80.34; h, 5.23; $-OCH_3$, 8.95.

A mixed melting point with a sample of this product obtained from Dr. H. H. Wasserman was not depressed. The infrared spectra were also identical.

α -Methyl- α, β, δ -triphenyl- $\triangle \beta, \delta$ -butenolide (XVIII). Into a flame dried 250 ml. round bottom flask was placed a mixture of sodium

hydride (0.4 g., 0.017 mole), methyl iodide (5 g., 0.035 mole), 25 ml. of dry dimethyl sulfoxide, and 10 ml. of dry benzene. The flask was flushed with oxygen free nitrogen and stirred magnetically for 5 minutes at room temperature. When solid (X), 3.12 g. (0.01 mole), was added an immediate yellow color was produced. A fairly rapid evolution of hydrogen occurred and the methyl iodide was observed to reflux. The opaque yellow solution became clear yellow after stirring for 15 minutes, after which an additional 5 g. of methyl iodide was added. The remaining color slowly faded. After stirring for a total of 2.75 hours the reaction mixture was filtered, poured into 500 ml. of water, and extracted with benzene. The organic phase was back washed with water, dried over sodium sulfate, and evaporated to dryness. The crude solid was recrystallized from methanol to give 2.48 g. of the product m.p. 116.5-118.5° and 0.25 g. of a second crop m.p. 112-116°, in 84% total crude yield. An analytical sample was recrystallized from methanol twice and had m.p. 118-119°, infrared absorption (KBr) 5.55μ . A mixed melting point with (X) was depressed, m.m.p. 96.5-123°.

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56.

Found: C, 84.51; H, 5.59.

3,4,5-Triphenyl-2-furyl Benzoate (XIX) A mixture of sodium hydride (0.17 g., 0.007 mole) and 30 ml. of dry dimethylformamide was stirred magnetically under a nitrogen atmosphere at room temperature. α,β,δ -Triphenyl- $\Delta^{\alpha,\beta}$ -butenolide (1.56 g., 0.005 mole) in 10 ml. of benzene was added dropwise over a 15 minute period. A yellow color formed. Benzoyl chloride (0.71 g., 0.005 mole, dried over CaH_2) in 5 ml. of benzene was then added dropwise over a 5 minute period,

discharging the color. Stirring was continued for an additional 45 minutes. The reaction mixture was filtered (the residue gave a strong chloride ion test), poured into 500 ml. of water and extracted with benzene. After drying over sodium sulfate the benzene solution was evaporated and the residue was recrystallized from benzene-methanol (5:1). There was obtained 0.9 g. of the benzoate, m.p. 198.5-199.5°. The crude second crop (0.7 g.) was recrystallized from methanol to give 0.18 g. of recovered starting butenolide, m.p. 122-125°.

The mother liquors from the recrystallizations were combined and evaporated to dryness, the residue (0.66 g.) was chromatographed on 20 g. of alumina with benzene. The first fraction afforded 0.64 g. of crude recovered butenolide, which when recrystallized from methanol gave 0.51 g., m.p. 125.5-126°. The total recovered butenolide was 0.69 g. (44%). The mother liquor on concentrating gave an additional 0.02 g. of the benzoate, bringing its total yield to 0.92 g. (44%).

Recrystallization of the benzoate from benzene raised the melting point to 199-199.5°, further recrystallization from this and other solvents did not change this range. A molecular weight value of 421 was obtained; calculated mol. wt., 416.5. A satisfactory elemental analysis could not be obtained; calcd. for $C_{29}H_{20}O_3$: C, 83.63; H, 4.84. Found: C, 84.47, 84.37; H, 5.04, 5.09. Material from a previous reaction (m.p. 197-198°) gave: C, 83.06; H, 4.89.

Infrared absorption showed single carbonyl absorption at 5.70μ (KBr). N.m.r. ($CDCl_3$), τ values: 1.85 (center of weak doublet, 2H); 2.67 (center of multiplet, 18H).

Hydrogenation of γ -Hydroxy- α,β,γ -triphenyl- $\Delta^{\alpha,\beta}$ -butenolide.

A one gram sample of the pseudo acid (XVII) was dissolved in 45 ml. of

ethyl acetate and hydrogenated at 25° with 0.2 g. of previously reduced Adams catalyst for 4 hours.

The catalyst was filtered (Celite) and the solution extracted with 10% sodium carbonate. The organic phase gave 0.1 g. of uncharacterized material (m.p. 127-138°). Acidification of the aqueous phase precipitated a solid which plated out on all glassware it came in contact with and, it was very hard to remove even with boiling benzene. Part of the precipitated acid was filtered to give 0.39 g., m.p. 201.5° dec.. An additional 0.26 g. of acid m.p. 189-194.5° dec. was obtained from the benzene extracts. The total recovered crude yield of acid was 64% (this moderate yield is accounted for in part by the extreme difficulty of removing the acid from the glassware). Two recrystallizations from ethanol and one from benzene-hexane gave an analytical sample of δ -hydroxy- α,β,γ -triphenylbutyric acid m.p. 207° dec. (gas evolution, clear melt), infrared absorption (KBr) 2.91 and 5.88 μ .

Anal. Calcd. for $C_{22}H_{20}O_3$: C, 79.49; h, 6.06.

Found: C, 79.47; h, 6.17.

A small sample of this acid was found to lose water when heated in an oil bath at 220°. The solidified material remelted at 162-176° and the infrared spectrum indicated that it was the corresponding triphenyl butenolide (identical spectrum with the material obtained in the Pt/C reaction below).

Hydrogenation of α,β,γ -Triphenyl- $\Delta^{9,10}$ -butenolide. Platinum on Charcoal. A 2 g. sample of (X) was dissolved in 65 ml. of ethyl acetate and hydrogenated at 26° over 0.4 g. of 5% Pt/C for 320 minutes. Hydrogen absorption had practically ceased after 223 ml. of hydrogen had

been taken up at the end of this period. The catalyst was filtered (Celite) and the solution evaporated to dryness. The residue was taken up in benzene and extracted with 10% sodium carbonate. The organic phase was dried over sodium sulfate, concentrated and diluted with hexane. There was obtained 1.59 g. (79%) of α,β,γ -triphenylbutanolide, m.p. 165-170°. This material was combined with some previously prepared material, using this same procedure, and recrystallized from benzene-hexane and then from aqueous ethanol to give an analytical sample m.p. 173-174°, infrared absorption (KBr) 5.67 μ . McRee and co-workers (60) have prepared another form of this butanolide which melts at 153°. Ivanov and Mladenova-Orlinova (61) gave m.p. 143-144° for still another isomer of this butanolide.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77.

Found: C, 83.94; H, 5.76.

Usual work up of the aqueous phase gave 0.08 g. (3.5%) of erythro α,β,γ -triphenylbutyric acid m.p. 132-140°. A recrystallization from benzene-hexane gave 0.05 g. of the acid m.p. 138-140.5°. The infrared spectrum in chloroform was identical to the acid described below.

Using Palladium on Charcoal. A 4 g. sample of (X) was dissolved in 70 ml. of ethyl acetate, 0.8 g. of 10% Pd/C was added and the mixture hydrogenated in a Parr apparatus under 44.5 p.s.i. for 23 hours. The catalyst was filtered (Celite) and the solution was concentrated and diluted with hexane. There was obtained 2.46 g. of erythro α,β,γ -triphenylbutyric acid m.p. 142-143°. Concentration of the mother liquor and saturating with hexene gave an additional 0.94 g. of the acid m.p.

140-141°. The total crude yield of acid was 84%. Two recrystallizations from benzene gave an analytical sample m.p. 144-145°, infrared absorption (KBr) 5.90 μ . Lednicer and Hauser (45) report the melting point of this erythro acid to be 137-140°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37; mol. wt., 316.

Found: C, 83.82; H, 6.41; neu. eq., 316.

Esterification of this acid (1.3 g.) with 20 ml. of anhydrous methanol and 4 drops of sulfuric acid at reflux for 5.5 hours, afforded 0.53 g. (98%) of the erythro methyl ester, based on recovered starting acid (39% conversion). Recrystallization from methanol gave 0.52 g. of the pure ester m.p. 164-164.5° (lit. (44) 159-160°). A molecular weight determination on this ester gave a value of 336. The calculated value for the ester is 330.

Using Adams Catalyst. Adams catalyst (0.2 g.) was prereduced in a glass hydrogenation apparatus in ethyl acetate. A solution of (X) (1.0 g., 0.0032 mole) in 10 ml. of ethyl acetate was added and the solution was hydrogenated for 25.75 hours. Hydrogen absorption had not stopped after taking up 360 ml. of hydrogen (equivalent to 5 moles of hydrogen per mole of butenolide), but the reaction was worked up. The catalyst was filtered (Celite) and the solution was extracted with 10% sodium carbonate. The acid free organic phase was dried and the solvent was removed by an air stream. There was obtained 0.31 g. (29.5%) of a dicyclohexylphenylbutenolide. Two recrystallizations from ethanol gave an analytical sample m.p. 209-212°, infrared absorption (KBr), strong carbon-hydrogen stretching vibrations at 3.46 and 3.55 μ , carbonyl absorption at 5.75 μ , aromatic stretching vibration at 6.71 and 6.91 μ ,

and lack of butenolide double bond absorption at $6.6.2\mu$.

The infrared absorption information in addition to the molecular weight and analytical data indicate that 2 of the 3 aromatic rings had been reduced in addition to the double bond of the lactone ring.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26; mol. wt., 326.5.

Found: C, 80.66; H, 9.28; mol. wt., 331.

The aqueous phase, after the usual work up and recrystallization from benzene-hexane, afforded as the first crop 0.4 g. (39.5%) of erythro α, β, γ -triphenylbutyric acid m.p. $145-147^\circ$. Recrystallization of the acid from benzene-hexane gave the erythro acid m.p. $140-143^\circ$, whose mixed melting point with previously prepared erythro acid was not depressed. The second crop of acid amounted to 0.15 g. (15%) of threo α, β, γ -triphenylbutyric acid m.p. $150-156^\circ$. Recrystallization of this acid from benzene-hexane raised the melting point to $155.5-158^\circ$. A neutralization equivalent of 315 was obtained for this acid; calculated molecular weight, 316. The recorded melting point for the threo acid is $159-160^\circ$ (45).

Saponification of 3,4,5-Triphenyl-2-furyl Benzoate. The ester (0.2 g.), 20 ml. of 10% sodium hydroxide and 3 ml. of ethanol was refluxed for 17 hours. The usual work up of the solution gave a quantitative yield of threo α, β -diphenyl- β -benzoylpropionic acid, m.p. $205-207^\circ$. Literature value is, m.p. $201-202^\circ$ (2). The residue from the recrystallization was shown, by infrared absorption, to consist of benzoic acid.

Transesterification of 3,4,5-Triphenyl-2-furyl Benzoate. The ester (0.1 g., 0.00024 mole), sodium ethoxide (0.000012 mole) in 25 ml. absolute ethanol and 20 ml. of ether was heated on a steam bath. The

ether was allowed to vaporize (to expel the air and prevent formation of pseudo acid (XVII)) after which the solution was refluxed for 11 hours. The excess solvent was evaporated to dryness in vacuo and the residue was extracted with benzene and water. The aqueous phase after the usual work up gave a trace (less than 0.01 g.) of the pseudo acid (XVII), indicated by an identical infrared spectrum in chloroform with that of the authentic pseudo acid.

The organic phase was dried and evaporated to dryness. The residue had the easily recognized odor of ethyl benzoate. The residue was recrystallized from ethanol to give 0.01 g. of the recovered benzoate (XIX), m.p. 199-200°. The mother liquor was evaporated to dryness; the infrared spectrum in chloroform had characteristic absorption indicating the presence of ethyl benzoate and α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide (compared with authentic samples for each). Recrystallization of the remaining crude lactone from methanol gave α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide m.p. 124-125°. The infrared spectrum (KBr) was identical to authentic triphenylbutenolide; also, a mixed melting point was not depressed.

An acid catalyzed transesterification attempt using 0.1 g. of the benzoate (XIX) and one drop of sulfuric acid in 25 ml. of absolute ethanol at reflux for 3.5 hours, resulted in a recovery of 90% of (XIX). No evidence for the presence of (X) was found in this reaction.

Saponification of α -Benzyl- α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide.

The butenolide (1 g.), 20 ml. of 10% sodium hydroxide and 10 ml. of ethanol was refluxed for 24 hours. The usual work up of the aqueous solution gave a quantitative yield of crude acidic material. Recrystallization of the crude acid from benzene-hexane gave 0.3 g. (28.5%) of

keto acid, m.p. 219-222° dec.. The second crop was mainly a pseudo acid, 0.75 g. (71.5%), which had m.p. 167-174°.

The first crop was recrystallized from benzene-methanol and benzene-ethanol to give an analytical sample of α -benzyl- α, β -diphenyl- β -benzoylpropionic acid, m.p. 224-225° dec., infrared absorption (KBr) 3.65, 5.70 and 6.08 μ . This acid does not give a dinitrophenylhydrazone with Shine's reagent (50).

Anal. Calcd. for $C_{29}H_{24}O_3$: C, 82.83; H, 5.75; mol. wt., 420.5.

Found: C, 82.64; H, 5.63; neu. eq., 420.

Recrystallization of the second crop 3 times from methanol and once from benzene-hexane gave an analytical sample of α -benzyl- α, β, γ -triphenyl- γ -hydroxybutanolide, m.p. 177-178°, infrared absorption (KBr) 3.00 and 5.72 μ . This pseudo acid does not give a dinitrophenylhydrazone with Shine's reagent (50).

Anal. Calcd. for $C_{29}H_{24}O_3$: C, 82.83; H, 5.75; mol. wt., 420.5.

Found: C, 82.74; H, 5.67; neu. eq., 415, 444.

Saponification of γ -Methoxy- α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide.

A solution of the pseudo ester (0.1 g., 0.00029 mole), 10 ml. of 10% sodium hydroxide and 5 ml. of ethanol was refluxed for 12 hours. Work up of this solution gave 0.09 g. of the previously described pseudo acid (XVII) m.p. 179-179.5° in 94% yield. A mixed melting point with the previously described analytical sample of this pseudo acid was not depressed; the infrared spectra were identical.

Saponification of α -Methyl- α, β, γ -triphenyl- $\Delta^{\beta, \gamma}$ -butenolide.

A solution of the butenolide (0.5 g., 0.00153 mole), 20 ml. of 10% sodium hydroxide and 5 ml. of ethanol was refluxed for 21 hours. Work up of this solution in the usual way gave 0.47 g. (89%) of α -methyl-

α, β -diphenyl- β -benzoylpropionic acid (XXI), m.p. 157-179°. Recrystallization of this acid from benzene-hexane gave 0.46 g. of product m.p. 172-177°. Two additional recrystallizations from benzene-hexane-methanol and one from benzene raised the melting point to 179-180°, infrared absorption (KBr) 3.30 and 5.95 μ . A satisfactory analysis could not be obtained for this acid; calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 77.96, 79.70; H, 6.02, 7.54.

Another preparation of this acid resulted in isolation of the pseudo form of this acid (same melting point) with infrared absorption (KBr) 3.07, 5.77 and 6.03 μ . This acid did not give a dinitrophenylhydrazone derivative using Shine's procedure (50). A neutralization equivalent for the pseudo acid gave high values of 355 and 359.

α -Benzylphenylacetic acid. This preparation was performed using the procedure of Hauser and Chambers (62) by permitting phenylacetic acid to react with benzyl chloride and sodium amide in liquid ammonia. The acid was obtained in 88.5% pure yield. A melting point of 90.5-91.5° was obtained from hexane-ether (lit. (62) 95.5-96.5°).

Methyl α -benzyl- α -bromophenylacetate. The method of Schwenk and Papa (63) was used to prepare this ester. α -Benzylphenylacetic acid was treated successively with thionyl chloride, bromine and methanol. A 72% overall yield of the ester was obtained by flash distillation, b.p. 170-175° at 1.3 mm.

Saponification of a sample of this ester with alcoholic sodium hydroxide for 3 hours gave a quantitative yield of the parent acid. Sodium fusion of a small sample of the acid gave a positive bromide ion test. An analytical sample of the acid had m.p. 152-153° from aqueous methanol, infrared absorption (KBr), 3.45 and 5.90 μ .

Anal. Calcd. for $C_{15}H_{13}O_2Br$: C, 59.04; H, 4.29.

Found: C, 58.57; H, 4.38.

trans α -Phenylcinnamic acid. Reaction of methyl α -benzyl- α -bromophenylacetate with the sodium salt of desoxybenzoin in ether (attempted alkylation) gave only dehydrohalogenation. The acid recovered had m.p. 173-175° (lit. (64) 172°).

PART I

SUMMARY

1. α, β, γ -Triphenyl- $\Delta^{\alpha, \beta}$ -butenolide was shown to undergo alkylation at both carbon (α position) and oxygen.
2. Benzoylation of α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide was shown to occur at oxygen.
3. Oxygen was shown to attack the α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide anion at the γ -position to give γ -hydroxy- α, β, γ -triphenyl $\Delta^{\alpha, \beta}$ -butenolide.
4. A proof of structure for γ -hydroxy- α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide was developed.
5. The configurations of the erythro and threo forms of α, β -diphenyl- β -benzoylpropionic acid, α, β, γ -triphenylbutyric acid and methyl α, β, γ -triphenylbutyrate were firmly established.
6. An improved synthesis of α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide was developed.

PART I

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PART II. REACTIONS OF OTHER BUTENOLIDES

DISCUSSION

In view of the success of the alkylation reactions and the moderate success of the acylation reactions on α, β, γ -triphenyl- $\Delta^{\alpha, \beta}$ -butenolide, described in Part I, it was of interest to extend these reactions to other butenolide systems. In addition, the scope and utility of these reactions were investigated using a wider variety of alkylating agents, and some different solvent systems. These studies were carried out with the following butenolides.

1. γ -Methyl- $\Delta^{\beta, \gamma}$ -butenolide (α -Angelica lactone)
2. γ -Methyl- $\Delta^{\alpha, \beta}$ -butenolide (β -Angelica lactone)
3. γ -Phenyl- $\Delta^{\beta, \gamma}$ -butenolide
4. γ -(p-Methoxyphenyl)- $\Delta^{\beta, \gamma}$ -butenolide
5. α -Methyl- γ -phenyl- $\Delta^{\alpha, \beta}$ -butenolide
6. α -Benzyl- γ -phenyl- $\Delta^{\beta, \gamma}$ -butenolide
7. α, γ -Diphenyl- $\Delta^{\alpha, \beta}$ -butenolide.

In addition, dimers of butenolides 2, 6 and 7 were also alkylated, and found to yield monomeric products. Dimers apparently of a different type, of butenolides 5 and 7, did not undergo alkylation under these same conditions.

Acylation reactions were also tried on 1 and 5 using some different procedures.

Preparation of γ -Phenyl- $\Delta^{\beta\gamma}$ -butenolide (I)

This compound was first prepared, although incorrectly formulated, by Biedermann (1) in 1891 and all who have worked with this compound up to the present seem to be in agreement on the difficulty of obtaining (I) in the pure state. Besides the low yields, the product is usually a dark red material when crude and does not give a colorless material by the usual recrystallization methods. In fact some of the early workers assumed that the product had a reddish color. Kugel (2) explored methods for improving the preparation of (I) (obtained by dehydrating β -benzoylpropionic acid with acetic anhydride at 100°) including steam distillation of the crude material which did give a 23% yield of the colorless product, the use of longer reaction periods, heating the reactants in a sealed tube at 100°, use of large excesses of acetic anhydride, and use of a carbon dioxide inert atmosphere all without much success. In addition the butenolide (I) is unstable and slowly decomposes upon standing in air.

In view of these difficulties a search for a better method of preparation led to the observation that the longer the heating was carried out the darker red the solution became and the more difficult it became to obtain a pure product. The recent use of sulfuric acid as a catalyst for this reaction also causes the mixture to darken in direct proportion to the amount of acid catalyst used. However, eliminating the sulfuric acid resulted in no conversion of the keto acid to the butenolide under the same conditions as employed by Kugel (2). The alternative was to lengthen the reaction time but to eliminate the heating.

This new procedure was found to give a purer product (although not completely colorless) and a higher yield than any other procedure or

modification reported in the literature. The general procedure consisted of warming a mixture of β -benzoylpropionic acid and a moderate excess of acetic anhydride, containing a small amount of sulfuric acid, to dissolve the keto acid. The mixture was then allowed to stand for 3 days. The resulting light orange solution upon cooling afforded a 81-87% yield of light yellow crystalline (I).

Other modifications tried consisted of varying the heating periods at 100° to reflux, use of milder acid catalysts including phosphoric acid, polyphosphoric acid, and benzenesulfonic acid; use of thionyl chloride or trifluoroacetic anhydride in place of acetic anhydride, use of a nitrogen atmosphere, and several combinations of these conditions. All of these procedures resulted in the usual low yield (5-60%), the highest of these being the dark red material. Unsatisfactory attempts to purify the dark red material consisted of flash distillation or sublimation both of which resulted in large losses of material due to decomposition. Steam distillation of the red material, however, resulted in an average recovery of about 50% of pure (I). The residue from the steam distillation consisted mostly of β -benzoylpropionic acid resulting from hydrolysis.

The recrystallized product could be kept in an evacuated dessicator for up to 6 months before appreciable hydrolysis occurred. The remaining product could be recovered by extracting the partly hydrolyzed material with hot hexane. The sublimed and steam distilled product was originally almost colorless but within one day the material had taken on a yellow color. The best recrystallized material had a light yellow color which within one week in vacuo had turned salmon pink but only on the exposed surface of the crystals. This pink color does not change

much until after standing for some time, when a yellow oil begins to form indicating that hydrolysis had occurred to a considerable extent.

It is interesting to note that these preparations have been very capricious and that the highest yields (60-87%) were obtained only when a single bottle of redistilled acetic anhydride was used. No difference between this anhydride and other bottles of acetic anhydride could be detected. In many attempts the reaction failed to give any butenolide, but by chilling the reaction mixture in some cases a small amount (0.5-3%) of a colorless high melting material could be isolated. Present evidence, which will be discussed in more detail later, indicates that this material is a dimer of butenolide (I).

Failure of these reactions to produce (I) was demonstrated by the following: a) chilling the crude reaction mixture and seeding with authentic (I) did not induce recrystallization when (I) was absent; b) removing the solvent in vacuo and extraction of the residue (which was usually a red solid if (I) was present) with hexane, followed by decantation of the solution deposited crystals of (I) immediately if it was present; and c) the characteristic, not unpleasant, odor of (I) indicated its presence or absence in the solvent free residue. Only small amounts of unchanged keto acid could be recovered from the reactions which failed. The solvent free, dark red thick oil, from the reactions which failed, could not be induced to crystallize.

Fang (3) has also observed these red amorphous residues from preparations of this butenolide, and reported that in addition to recovering some keto acid, a dimer which was colorless and a red dimer was also present in these residues.

Preparation of α, α -Dibenzyl- γ -phenyl- $\Delta^{\beta, \gamma}$ -butenolide (II)

This series of alkylations was done in hydrocarbon solvents before the procedure using dimethyl sulfoxide described in Part I was developed. Procedures for the preparation of (II) are summarized in Table I. The increase in yield with increasing boiling point of hydrocarbon solvents Table I (reactions 1 and 2) was found to be the same as previously described in Part I for similar reactions. However, in contrast to the high yield of product obtained using benzyl benzenesulfonate described in Part I, this reagent under almost identical reaction conditions failed to undergo any reaction with γ -phenyl- $\Delta^{\beta, \gamma}$ -butenolide (I), the sulfonate being recovered in quantitative yield.

Attempts to monobenzylate (I), indicated in Table I (reactions 5 and 6) using equivalent amounts of butenolide, base and alkylating agent, resulted only in the isolation of reduced yields of the dibenzyl derivative (II). Apparently the first benzyl substitution activates the remaining α -hydrogen so that it is removed and the anion alkylated a second time at the expense of any unsubstituted anion which may be present.

A Michael dimer, obtained from the lithium aluminum hydride reduction of α -benzylidene- γ -phenyl- $\Delta^{\beta, \gamma}$ -butenolide (described in detail later), when allowed to react with benzyl chloride and sodium hydride in refluxing toluene for 3 hours, gave a 55% yield of this same monomeric debenzyl butenolide (II).

Reactions 1-6, in Table I, were accompanied by considerable amounts of dark tarry material which accounts in part for the low yields. Also some uncharacterized acidic material could be isolated from some of these reactions, but no β -benzoylpropionic acid could be detected.

TABLE I
 ALKYLATIONS OF γ -PHENYL- $\Delta^{2,3}$ -BUTENOLIDE

	Alkylating Agent	Base	Solvent	Temp. C ^o	Time hrs.	Yield %
1.	$\phi\text{CH}_2\text{Cl}$	NaH^a	Toluene	Reflux	3.75	44 (II)
2.	$\phi\text{CH}_2\text{Cl}$	NaH	Benzene	Reflux	2.5	11 (II)
3.	$\phi\text{CH}_2\text{Cl}$	NaNH_2	$\text{NH}_3\text{-Et}_2\text{O}$	-40	1.25	8.5 (II)
4. ^b	$\phi\text{CH}_2\text{Cl}$	NaH	Diglyme	Reflux	3.75	6.5 (II)
5. ^b	$\phi\text{CH}_2\text{Cl}$	NaH	Toluene	Reflux	2.5	3 (II)
6.	$\phi\text{CH}_2\text{OSO}_2\phi$	NaH	Toluene	70 ^c	1.25 ^c	0 ^d
7.	$(\text{Me})_2\text{SO}_4$	NaH	Toluene	Reflux	3.5	20 ^e (V)

a 50% in oil

b monobenzylation attempt

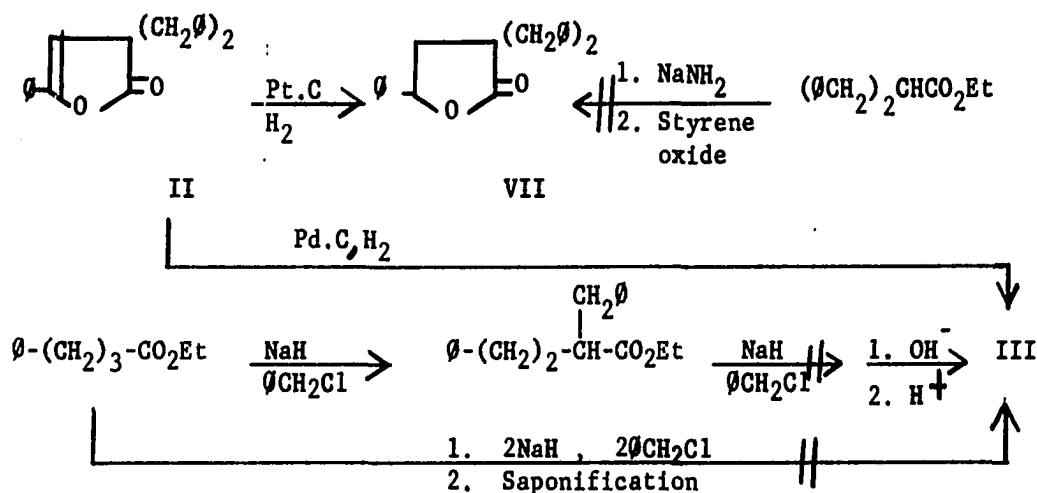
c after formation of butenolide anion

d quantitative recovery of alkylating agent

e no butenolide recovered

Proof of Structure for α,α -Dibenzyl- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide (II)

Unsuccessful attempts at a proof of structure for (II) using the following two routes failed at the indicates steps.

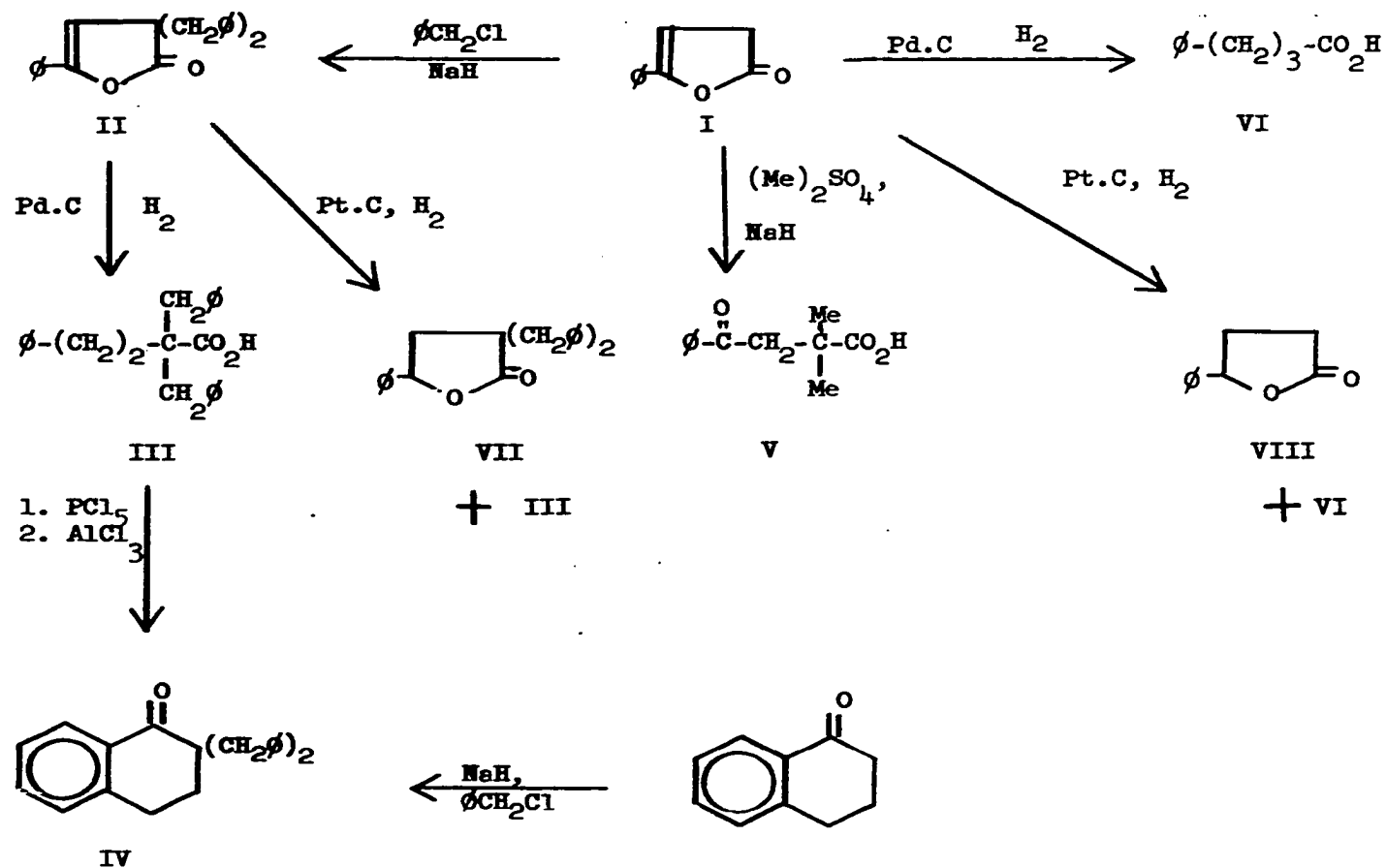


The following series of reactions, however, provided a proof of structure for (II) (Fig. 1). Hydrogenation of (II) in ethyl acetate using Pd/C under 43 p.s.i. gave a 96.5% crude yield of α,α -dibenzyl- γ -phenylbutyric acid (III). Conversion of (III) to the acid chloride using phosphorous pentachloride followed by inverse addition to aluminum chloride gave an 81% yield of 2,2-dibenzyl-1-tetralone (IV). An alternative procedure consisted of treating the molten acid (III) briefly with polyphosphoric acid which gave a 19.5% yield of the tetralone (IV) and a large amount of recovered acid (III).

The dibenzyl tetralone (IV) was also obtained from the benzyla-tion of tetralone, using sodium hydride and benzyl chloride in refluxing benzene, in 74.5% yield. Although all attempts to prepare one of the usual carbonyl derivatives of (IV) failed, a mixed melting point with the material prepared from (II) was not depressed.

FIGURE 1

FLOW SHEET FOR REACTIONS OF (I)



Methylation of γ -Phenyl- $\Delta^{\beta\gamma}$ -butenolide

The first attempt to prepare (X) (Fig. 2) from γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (I) using sodium hydride and dimethyl sulfate in refluxing toluene (Table I, reaction 7) resulted in the isolation of α,α -dimethyl- β -benzoylpropionic acid (V) in 20% yield. None of the expected butenolide was found but it must have been a precursor to the formation of the acid.

The reaction of α -methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (IX) with methyl iodide and sodium hydride in DMSO gave a crude product the infrared spectrum of which indicated the presence of (X) with carbonyl absorption at 5.55μ . The crude product was chromatographed on alumina. The purified oil that was obtained would not crystallize, but after standing about a week the keto acid (V) was obtained in 13% yield. The alumina from the chromatography was not examined for any of this acid but it could have promoted hydrolysis of the product.

An identical reaction in DMSO, but followed by chromatography on Florisil, gave the same oily butenolide (X) in 24% yield which also hydrolyzed after standing 7 days. A dimer of (IX) was also isolated from the chromatography in 36% yield. Although both of these reactions were performed with crude α -methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (IX) the infrared spectrum of this crude oil did not show any of the dimer (which is also insoluble in the oily monomer) to be present prior to the start of these reactions. Precautions were taken during the reaction to exclude oxygen, which promotes the formation of this dimer. The dimer must have originated from unreacted (IX) during the work up or later in the purification steps. The nature of this dimer will be discussed later.

Florisil was found not to promote hydrolysis of (X), since none of the keto acid (V) was isolated from the Florisil.

Of all the butenolides used or prepared in this work (X) was the most susceptible to hydrolysis. Rothstein and Saboor (4) reported a melting point of 45° for (X) but several attempts failed to induce the chromatographed product described above to crystallize.

Preparation of γ -(p-Methoxyphenyl)- $\Delta^{\beta,\gamma}$ -butenolide

In contrast to the difficulties encountered with the preparation of the parent γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide (I), the procedure of El-Assal and Shehab (5) was found to give this methoxy derivative conveniently. A Norite treatment prior to recrystallization was found to give a light yellow product rather than the red material usually obtained by recrystallization. This compound is also more stable than γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide (I), and has been kept in bottles for a year before appreciable hydrolysis had occurred.

An epoxidation of this butenolide using perbenzoic acid indicated that the reaction occurred but that the product was a mixture of uncharacterized acids. Similar results have been reported by Gardner (6).

Benzylation of γ -(p-Methoxyphenyl)- $\Delta^{\beta,\gamma}$ -butenolide

Procedures for these benzylations are summarized in Table II. The variety of conditions used for these benzylation reactions give a clear indication of the effect the solvent has on the course of this reaction.

The clear superiority of DMSO and dimethylformamide (DMF), over

TABLE II

 BENZYLATIONS OF γ -(p-METHOXYPHENYL)- $\Delta^{\beta,\gamma}$ -BUTENOLIDE

	Alkylating Agent	Base	Solvent	Temp. C°	Time hrs.	α,α -Dibenzyl Derivative %
1.	OCH_2Cl	NaH	DMSO	Room	1.75	39
2.	OCH_2Cl	NaH	DMF- OH (1:1)	Reflux	1.75	26
3.	OCH_2Cl	NaH	DMF	Room	1	14
4.	OCH_2Cl	NaH	Toluene	Reflux	1	5
5.	OCH_2Cl	NaH	Benzene	Reflux	2	47 ^a
6.	OCH_2Cl	NaNH_2	Et_2O	Room	1	0
7.	OCH_2Cl	KOBu_t	Benzene	Reflux	2	22 ^a

a only keto acid obtained by hydrolysis of starting material during reaction

hydrocarbon solvents, under considerably milder conditions is quite evident (39 and 26% yield versus 5%, respectively). While the overall yields are not high, being accompanied by tars, the reaction mixtures in reactions 1-3 of Table II have considerably less tars associated with them than reaction 4. Some comments applicable to DMSO have already been described in Part I. While some heat is generated using DMSO, comparable reactions using DMF have been observed under almost identical reaction conditions to be considerably more exothermic (approx. 20° temperature rise). With the more sensitive butenolides the higher the reaction temperature employed the greater the tar formation appears to be. The reactions using DMSO in most cases are also accompanied by the production of a small amount of smelly material which resemble sulfides or mercaptans, however, this material has not been isolated and does not appear to have any effect upon the reaction product or its isolation.

The structure of the butenolide that is obtained from these benzylation reactions, while not established by independent synthesis, had infrared absorption (5.57 μ) that is characteristic for $\Delta^{\beta,\gamma}$ -butenolides. It is assumed that the methoxy butenolide would undergo benzylation at the α -position to yield the α,α -dibenzyl derivative in the same manner as previously described for (I).

Preparation of α -Methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (IX)

Ramirez and Rubin (7) have reported the preparation of both isomeric forms of α -methyl- γ -phenyl butenolide. Treatment of α -methyl- β -benzoylpropionic acid with acetic anhydride and sulfuric acid catalyst was reported to give the $\Delta^{\alpha,\beta}$ -isomer, whereas, acetic anhydride alone was reported to give the $\Delta^{\beta,\gamma}$ -isomer. Use of their

procedure, in this work, in an attempt to prepare the $\Delta^{\beta,\gamma}$ -isomer gave a product which had m.p. 229-230°, but which corresponds to their $\Delta^{\alpha,\beta}$ -isomer which had m.p. 226-227°. A molecular weight determination on this compound is actually a dimer. A more complete discussion of this and other dimers will be treated more fully later.

The reaction of the keto acid with acetic anhydride under a nitrogen atmosphere, however, gave a thick light-yellow oil which would not crystallize. A molecular weight determination on this oil indicated that it was almost completely a monomer of the butenolide and infrared absorption at 5.69 μ indicated it to be the $\Delta^{\alpha,\beta}$ -form. When this oil was exposed to air it slowly precipitated solid which was identical to the oxidative dimer obtained in the first attempt described above.

Preparation of α -Benzyl- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide (XII)

Thiele and Mayr (8) prepared both isomers of this butenolide and reported that the $\Delta^{\beta,\gamma}$ -isomer, m.p. 100-101°, is the labile form and that heating in acetic anhydride converts it into the more stable $\Delta^{\alpha,\beta}$ -isomer m.p. 67°. In this work heating α -benzyl- β -benzoyl-propionic acid with acetic anhydride under a nitrogen atmosphere gave the product (XII) m.p. 100-101° with infrared absorption at 5.57 μ . When this reaction was performed in the presence of air, or the butenolide (XII) heated above the melting point for short periods, a material was obtained which melted above 200°. It is probably the same type of dimer as the other high melting substances which are obtained in this same way, but due to the lack of material this substance was not examined further.

Preparation and Proof of Structure of α -Methyl- α -benzyl- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide (XI)

α -Methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (IX) was treated with benzyl chloride and sodium hydride in DMSO at room temperature to give a 52% yield of the α -benzylated product (XI) (Fig. 2).

The proof of structure consisted of treating the alternate compound, in this case, α -benzyl- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide (XII) with methyl iodide under the same conditions as above to give a 74.5% yield of this same product (XI). Infrared spectra of both products were identical and a mixed melting point showed no depression.

Butylation of α -Methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide

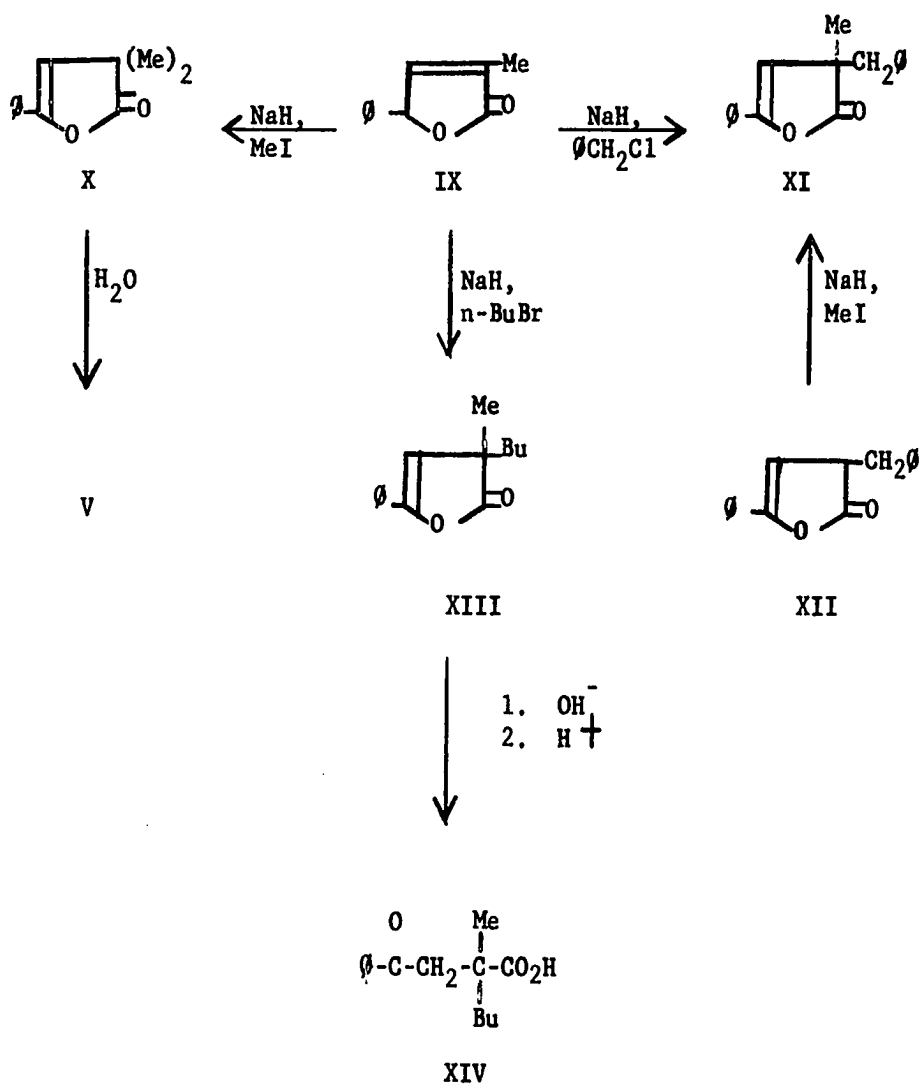
Reaction of α -methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (IX) with n-butyl bromide, sodium hydride and DMSO at room temperature gave a 39% yield of α -methyl- α -butyl- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide (XIII). Although the structure of (XIII) was not proved, it had infrared absorption at 5.56μ that is consistent with other $\Delta^{\beta,\gamma}$ -butenolides. In addition a 12% yield of α -methyl- α -butyl- β -benzoylpropionic acid (XIV) was isolated, the result of some accidental saponification of (XIII) taking place during the reaction. The intentional saponification of (XIII) gave the same acid. That this acid was a keto acid was demonstrated by formation of a dinitrophenylhydrazone using Shine's reagent (9). This is also indirect evidence for the butyl group occupying the α -position of (XIII). Also from this butylation reaction a 0.6% yield of a dimer of (IX) was also isolated.

Preparation of α,γ -Diphenyl- $\Delta^{\alpha,\beta}$ -butenolide

When α -phenyl- β -benzoylpropionic acid was heated with acetic

FIGURE 2

FLOW SHEET FOR REACTIONS OF (IX)



acid and sulfuric acid according to the method of Baddar and Sherif (10) the compound reported by them was obtained and had m.p. 286° dec. This material would not undergo benzylation using benzyl chloride and sodium hydride in either refluxing toluene or refluxing DMF. A Grignard reaction with this material also failed and it was suspected that this product as well as the material of Baddar and Sherif is not the claimed $\Delta^{\alpha,\beta}$ -butenolide, but rather a dimer.

A milder dehydration of the keto acid using acetic anhydride gave a material m.p. 233.5 - 234.5° in addition to a 290° dec. material (identical to the 286° dimer obtained above). This 234.5° material was also a dimer as indicated by a molecular weight determination, but must be different from the product obtained by the Baddar and Sherif (10) method. The 234.5° dimer can be alkylated easily and dissolves readily in benzene without thermochromic behavior in contrast to the 290° dimer. The nature of these dimers will be discussed more fully later.

The authentic diphenyl butenolide was obtained using the procedure of Yates and Clark (11), which requires heating the above keto acid and acetic anhydride under a nitrogen atmosphere. The crude oil which is obtained sometimes solidifies. This crude butenolide when freshly prepared is monomeric, but when exposed to air for purposes of recrystallization gives the dimers (234.5 and 290° dec.) described above. No further purification procedures were successful on this crude product and it was used in this state.

Benylation of α,δ -Diphenyl- $\Delta^{\alpha,\beta}$ -butenolide

Reaction of α,δ -diphenyl- $\Delta^{\alpha,\beta}$ -butenolide with benzyl chloride and sodium hydride in DMSO at room temperature gave a 77.5% yield

of α,δ -diphenyl- α -benzyl- $\Delta^{B\delta}$ -butenolide. In addition an 18% yield of α -benzyl- α -phenyl- β -benzoylpropionic acid, resulting from saponification of the diphenyl benzyl butenolide during the reaction, was also isolated.

The dimer (234.5⁰) derived from the diphenyl butenolide was found to react under the same conditions as above to give the monomeric benzyl butenolide derivative in 63.5% yield. Also the same keto acid was isolated in 15% yield.

An independent proof of structure for this benzyl butenolide was not attempted, but infrared absorption at 5.60 μ is consistent with other $\Delta^{B\delta}$ -butenolides.

The intentional saponification of the benzyl butenolide gave the same keto acid as that obtained in the accidental saponifications above. This acid does not form a dinitrophenylhydrazone using Shine's reagent (9). The NMR spectrum for this acid is in agreement for the benzyl group occupying the α position. For example, the typical ortho hydrogen absorption of aryl ketones was found at 2.08 τ , the β -methylene hydrogens and the two hydrogens of the benzyl group were found together as a singlet at 6.37 τ (any location other than α for the benzyl group would lead to splitting of the peaks for the remaining α and β aliphatic hydrogens).

Preparation of α,δ -Diphenyl- α -cyclopentyl- $\Delta^{B\delta}$ -butenolide

In view of the success obtained with the benzylation of the dimer (234.5⁰) of diphenyl butenolide, although the monomer gave a slightly higher yield, this reaction was performed using this dimer which is easier to work with than the monomer.

The reaction of the dimer with cyclopentyl bromide and sodium hydride in DMSO at room temperature gave a 47% yield of the cyclopentyl derivative. A proof of structure for this cyclopentyl derivative was not attempted, but infrared absorption at 5.60μ is consistent with other $\Delta^{\beta,\gamma}$ -butenolides. In addition, evidence for the cyclopentyl group being at the α position was obtained by saponification of the butenolide to give the corresponding pseudo acid which form only from γ -keto acids.

Preparation and Isomerization of γ -Methyl- $\Delta^{\beta,\gamma}$ -butenolide (XV)

The procedure of Helberger, Ulubay and Civelekoglu (12) was used which requires a slow distillation of a mixture of levulinic acid and phosphoric acid under reduced pressure, to give an excellent yield of γ -methyl- $\Delta^{\beta,\gamma}$ -butenolide (α -angelica lactone). The α and β designations of angelica lactone refer to the boiling points of the isomers. The low boiling isomer is called α and the higher boiling isomer, the $\Delta^{\alpha,\beta}$ -isomer, designated β . Using this procedure a 67.5% yield of (XV) (Fig. 3) was obtained from commercial levulinic acid.

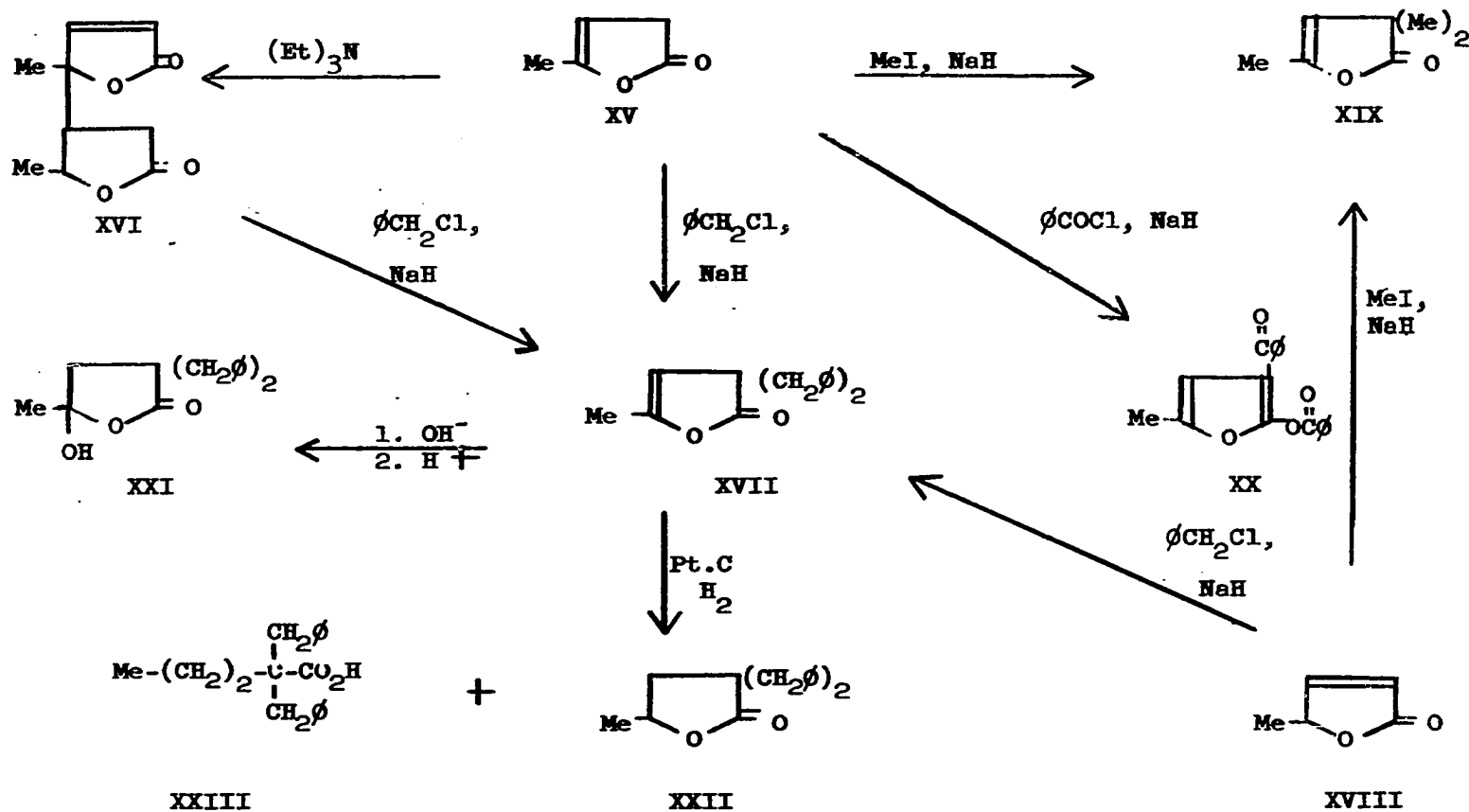
The isomerization of α -angelica lactone (XV) using the method of Ramirez and Rubin (7) was attempted with triethylamine at reflux temperature but only a high boiling thick oil was obtained. None of the expected α -methyl- $\Delta^{\alpha,\beta}$ -butenolide (β -angelica lactone) was isolated. A molecular weight determination on this oil gave a value of 201 indicating that it was a dimer. This material was shown to be the Michael dimer (XVI) and will be discussed more fully later.

Preparation of α,α -Dibenzyl- γ -methyl- $\Delta^{\beta,\gamma}$ -butenolide (XVII)

Of the 3 different reactions employed for the preparation of

FIGURE 3

FLOW SHEET FOR REACTIONS OF (XV)



(XVII) from α -angelica lactone (XV), as indicated in Table III (reactions 1-3), only the reaction using DMSO was successful.

The proper choice of solvent for recrystallization of (XVII) was found to affect the yield of (XVII) quite markedly. For example using benzene-hexane for recrystallization a 55% yield of pure (XVII) was obtained. However, if ethanol was used for recrystallization (in an almost identically run reaction) only a 17% yield of (XVII) was obtained along with a large amount of an oil which would not crystallize when seeded with pure (XVII). In addition to containing some butenolide (XVII), this oil also contained 2 other components designated "A" and "B". A crystalline solid was later obtained in pure form from this oil (see experimental section for details). An analysis and NMR spectrum of this solid indicated that it was ethyl α,α -dibenzyllevulinate (component A). The formation of this ester indicates that the butenolide (XVII) in the presence of alcohol for extended periods of time (approx. 3 days) can undergo hydrolysis and esterification (or alternatively transesterification) under relatively mild conditions (small amounts of benzyl chloride present).

It was independently demonstrated that these oily by-products were not present in the freshly prepared crude reaction mixtures. For example examination by vapor phase chromatography of the crude (free of acidic hydrolysis products) reaction mixture, in benzene, (Table III, reaction 1, prior to recrystallization) indicated that only the product (XVII) was present.

Saponification of a sample of the chromatographed ethyl ester (as an oil) gave a 94% yield of the pseudo acid α,α -dibenzyl- γ -methyl-

TABLE III

ALKYLATIONS OF γ -METHYL- $\Delta^{\beta\gamma}$ -BUTENOLIDE

	Alkylating Agent	Base	Solvent	Temp. C°	Time hrs.	Yield %
1.	CH_2Cl	NaH	DMSO	Room	3.5	55 (XVII)
2.	CH_2Cl	NaH	Benzene	Reflux	3.5	0
3.	CH_2Cl	NaOMe	Benzene	Reflux	2	0
4.	MeI	NaH	DMSO- OH	Room	2	81 (XIX)
5.	COCl^a	NaH	DMF	Room	4	6.5 (XX)
6.	COCl^a	NaH	DMF- OH	Room	2	6.3 (XX)
7.	CO_2Me^a	NaH	DMSO	Room	3.5	0

a acylating agent

γ -hydroxybutanolide (XXI). The pseudo acid (XXI) was also obtained in quantitative yield from saponification of butenolide (XVII).

The benzylation of β -angelica lactone (XVIII), under essentially the same conditions as employed for α -angelica lactone, and recrystallization from ethanol gave a 20.5% yield of the dibenzyl derivative (XVII) as well as the same large amount of oil. Vapor phase chromatography of the oil, after chromatography on alumina, indicated that the ethyl ester of debenzyllevulinic acid (13%) and component "B" (see experimental section) were present in a ratio of 1:1.6. One of the fractions from the alumina chromatography was almost pure (96%) component "B" and the rest was the ethyl ester already mentioned. The infrared spectrum of this "B" component was practically superimposable on that of the ethyl ester. An NMR spectrum of this fraction of "B" material was consistent with benzyl α,α -dibenzyllevulinate. The method of formation of this "benzyl ester", however, remains questionable at this time.

Benzylation of the Michael dimer (XVI), as described above for α -angelica lactone, followed by recrystallization from methanol, gave 17% of the dibenzyl monomeric (XVII) and an oil. In this case the chromatography and vapor phase chromatography of the oil indicated that only (XVII) and the "B" component were present. One fraction from the column chromatography consisted only of the "B" component and was saponified to give the same pseudo acid (XXI) as that obtained from the parent butenolide (XVII).

In summary, the formation of the same product from benzylation of α -angelica and β -angelica lactones (the first alkylation run using

both isomers of a butenolide) indicate that both isomers react through the same intermediate anion. The alkylation of the Michael dimer (XVI) probably occurs by way of this intermediate anion (by way of a retro-grade Michael reaction) also.

Proof of Structure for α,α -Dibenzyl- γ -methyl- $\Delta^{\beta,\gamma}$ -butenolide

The hydrogenation of this dibenzyl butenolide (XVII) using Pt/C in ethyl acetate at atmospheric pressure (Fig. 3) gave an 83.5% yield of α,α -dibenzyl- γ -methylbutanolide (XXII) in addition to a 14% yield of crude α,α -dibenzylvaleric acid (XXIII).

The benzylation of γ -valerolactone using benzyl chloride and sodium hydride in DMSO-benzene gave a 63% yield of the butenolide (XXII) which showed no depression of the mixed melting point with the material prepared above. In addition a 16% yield of cis stilbene, apparently formed by self condensation of benzyl chloride, was also obtained.

Preparation of α,α,γ -Trimethyl- $\Delta^{\beta,\gamma}$ -butenolide (XIX)

Methylation of α -angelica lactone (XV) (Table III, reaction 4) using methyl iodide and sodium hydride in DMSO gave an 81% crude yield of the known butenolide which distilled at 82-83° at 41 mm. This trimethyl butenolide was somewhat volatile at room temperature and pressure.

Methylation of β -angelica lactone (XVIII) (Fig. 3) under essentially the same conditions as above gave a 42% crude yield of the trimethyl butenolide (XIX).

Alkylation Failure in DMSO

An attempt to alkylate α -methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide

(IX) with 3 β -tosyloxycholestane using sodium hydride in DMSO at room temperature for 2 hours resulted in a 93% recovery of the tosylate. The same reaction at 100° gave a mixture of Δ^2 and Δ^3 -cholestene in 72% yield, and a 26% yield of 3 α -cholestanol, which was determined by column and vapor phase chromatography.

The procedure of Nace (13), which requires heating a mixture of the tosylate in DMSO at 100° for 5 hours, was used to prepare an authentic mixture of the Δ^2 and Δ^3 -cholestene for comparison with the above mixture by vapor phase chromatography.

A blank determination was run on the tosylate, in exactly the same manner as the alkylation attempt but excluding the butenolide, and resulted in the formation of the cholestenes as well as approximately 5% of 3 α -cholestanol (determined by infrared absorption). In this case the 3 α -cholestanol must arise from displacement by hydroxide ion (from NaOH present in the NaH) on the tosylate. The relatively low yield of the cholestanol in this case does not preclude the formation of some O-alkyl product which is then displaced by hydroxide ion at a later stage of the reaction or during the work up.

While this is the only failure in this study using DMSO, the failure lies in the relative ease with which DMSO promotes the elimination of toluenesulfonic acid from the tosylate.

Observations of γ -Keto Acids

It was noted during this study that the γ -keto acids used in the preparations of the butenolides, as well as the γ -keto acids obtained by saponification of the alkylated products gave different types of carbonyl absorption. Some of the γ -keto acids exhibited a single

broad absorption for the 2 carbonyl functions, others gave carbonyl absorption for both the ketone carbonyl and carboxylic acid groups, still others existed in the cyclic pseudo acid form in which hydroxyl and single ester carbonyl absorption was found. Some acids could be isolated in both the open γ -keto form and the cyclic pseudo form. These results are summarized in Table IV.

Of the 7 pseudo acids encountered in this work all (except the pseudo acid of α,α -dimethyl- β -benzoylpropionic acid) were found to contain at least one benzyl or phenyl group on the α -carbon and with one exception, the pseudo acid of α,β -diphenyl- β -benzoylpropionic acid (Part I) the other α position also contained a substituent other than hydrogen. Other acids which fulfill the above conditions but for which no pseudo acid had been detected include α -benzyl- β -benzoylpropionic acid, α -phenyl- β -benzoylpropionic acid, α -benzyl- α -phenyl- β -benzoylpropionic acid and the very similar α -benzylidene- β -benzoylpropionic acid.

It is also of interest to note that these alkylation reactions of butenolides provide a reasonable route to α,α -disubstituted- γ -keto acids (after saponification).

Butenolide Dimers

Some related material has been discussed in Part I.

From the very beginning, studies of dehydrations of saturated and unsaturated- γ -keto acids have given various high melting products. For example, Thiele and Straus (14) describe a dimer obtained from α -phenyl- γ -benzyl- $\Delta^{\alpha,\beta}$ -butenolide with m.p. 193° which could be saponified to give α,δ -diphenyllevulinic acid. The dimer was also found

TABLE IV

CARBONYL ABSORPTION FOR VARIOUS γ -KETO ACIDS

Acid $\begin{array}{c} \text{O} \quad \text{R}^3 \quad \text{R}^1 \\ \parallel \quad \quad \\ \text{R}^4 - \text{C} - \text{CH} - \text{C} - \text{CO}_2\text{H} \\ \quad \quad \quad \\ \quad \quad \quad \text{R}^2 \end{array}$				Carbonyl Absorption in Microns		
R ⁴	R ³	R ²	R ¹	Keto Acid Form		Pseudo Form
Me	H	H	H	5.82**		
Me	H	Me	Me	5.86		
Me	H	Be	Be			5.70
Ø	H	H	H	5.90*		
PMP	H	H	H	5.85*	5.98*	
Ø	H	Be	Be	5.85	5.92	5.75
Ø	H	Me	Me	5.85s	5.95	5.68
Ø	H	Be	H	5.85	5.95	
Ø	H	ØCH=		5.97		
Ø	H	Me	H	5.86	5.96	
Ø	H	Me	Bu	5.94		
Ø	H	Ø	H	5.98		
Ø	H	Ø	Be	5.90		
Ø	H	Ø	Cp			5.73
Ø	Ø	Ø	H [#]	5.87	5.97	5.66
Ø	Ø	Ø	Be [#]	5.70	6.07	5.71
Ø	Ø	Ø	Me [#]	5.93*		5.77

results from Part I

Unmarked values in KBr

* in CHCl_3

** neat

Me = methyl

 $\emptyset$ = phenyl

PMP = p-methoxyphenyl

Be = benzyl

Bu = n-butyl

Cp = cyclopentyl

s = shoulder

to reduce Tollens reagent. No structure was proposed for this dimer.

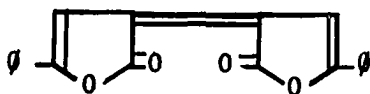
Pechmann (15) in 1882 first prepared a red uncharacterized material from cyclization attempts on β -benzoylacrylic acid. A similar substance was prepared by Kugel (2), Thiele and Sulzberger (16), Pummerer and Buchta (17), and several others; this material became known as "Pechmann's Dye" which was described as having structure (XXIV). This structure and the controversial evidence which had accumulated in the literature over this substance was reviewed in great detail by Fang (3) and finally proved by him to be correct.

Kugel (2) describes 4 high melting products, obtained from reactions on β -benzoylpropionic acid, a red substance which sublimes when heated (assumed by him to be XXIV), a yellow substance obtained by saponification of the red substance followed by reclosure, which also sublimes when heated (assumed to be an isomer of the red substance); a colorless compound (m.p. 227°) obtained as a by-product from the preparation of γ -phenyl- $\triangle^{\beta\gamma}$ -butenolide (assumed to be an isomer of the butenolide), and another colorless compound (m.p. 192°) obtained by reaction of β -benzoylpropionic acid with benzoyl chloride.

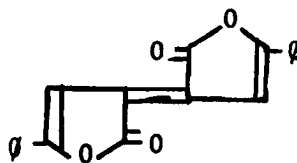
Fang (3) assigned the trans structure (XXV) to Kugel's (2) red compound and structure (XXVI) (unproved) to the 227° material. In this connection he also prepared a similar compound (structure unproved), to which he assigned structure (XXVII). Bogart and Ritter (18) assigned structure (XXVIII) to Kugel's yellow material. Kugel assumed (poor analysis) that his 192° material was formed by loss of a molecule of water from the α -hydrogens of one butenolide molecule and the carbonyl oxygen of another butenolide molecule; no other work on this material

seems to have been reported. In view of present chemical knowledge Kugel's proposed formation of this 192° material cannot possibly be correct.

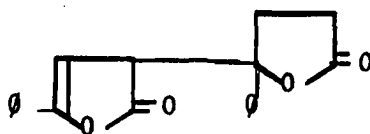
The red color associated with the preparation of γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide has been shown spectroscopically by Fang (3) to contain the "Pechmann Dye" (XXIV).



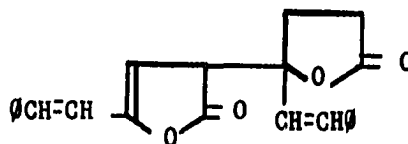
XXIV



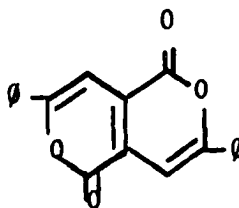
XXV



XXVI



XXVII

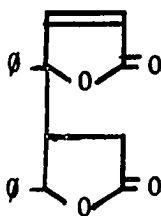


XXVIII

It has already been mentioned in this work that some attempted preparations of γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide gave instead very low yields of a colorless high melting material. The highest yield of this material (3%) was obtained using the procedure of Ramirez and Rubin (7) in which β -benzoylpropionic acid was treated with an acetic anhydride, acetic acid and sulfuric acid mixture at room temperature for 36 hours.

This material, which was the only product isolated, had, after repeated recrystallization from benzene m.p. $243-243.5^{\circ}$ dec., and showed carbonyl absorption at 5.73μ which indicated that the material was a $\Delta^{\alpha,\beta}$ -butenolide. Molecular weight determinations gave values of 322 and 323 indicative of a dimer. This material is probably the same as the 227° material prepared by Fang (3) in 2% yield, who repeated Kugel's (2) procedure of working over the steam distillation residue from the preparation of γ -phenyl- $\Delta^{\alpha,\gamma}$ -butenolide. Fang's 227° material was found to have the same properties as Kugel's material.

An NMR spectrum of this 243.5° dec. material indicated that it was a Michael dimer. The characteristic α and β hydrogens of the butenolide ring were found to absorb at 4.25 and 2.22τ respectively (both were doublets). The 4 hydrogens of the butenolide ring were not separated but were bunched over the range $6.9-8.5\tau$. The integrated hydrogen count indicated 16 hydrogens. On the basis of the NMR and infrared spectrum it is now possible to reassign Fang's structure (XXVI) for this material as structure (XXIX).

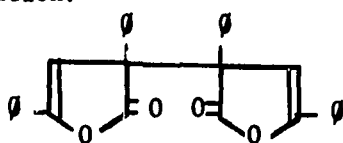


XXIX

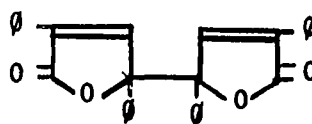
A dimer derived from α,γ -diphenyl- $\Delta^{\alpha,\beta}$ -butenolide has also received considerable attention in the literature. For example, Hamm and Lapworth (19) prepared a material, which was previously described by Anschütz and Montford (20) as having m.p. 288° . Hamm and Lapworth

found that this material was difficult to saponify and that it gave the odor of phenylacetic acid upon work up of the basic solution. Pummerer and Buchta (17) proposed structure (XXX) for this material. Waters (21) reviewed the literature on this material and also on the basis of the general resistance to saponification of $\Delta^{\alpha,\beta}$ -butenolides, infrared absorption, thermochromic behavior, and formation of phenylacetic acid (indicated by paper chromatography) when saponified reassigned the structure of this material as (XXXI). As late as 1960 this 288° material was still being incorrectly described by Baddar and Sherif (10) as monomeric α,γ -diphenyl- $\Delta^{\alpha,\beta}$ -butenolide. Davey and Tivey (22) also describe this material as the monomeric $\Delta^{\alpha,\beta}$ -isomer. Davey and Tivey considered the possibility that this 288° material was a dimer, but their molecular weight determination by the Rast method was complicated by the limited solubility of this compound. Yates and Clark (11) have shown that the authentic α,γ -diphenyl- $\Delta^{\alpha,\beta}$ -butenolide upon standing in air is converted into the oxidative dimer (XXXI) (Waters has also observed this), however, (as contrasted to the results of Waters, and Hamm and Lapworth) they find that saponification of the oxidative dimer (XXXI) gives only α -phenyl- β -benzoylpropionic acid and acetophenone (yields of these two products were not specified).

Yates and Clark (11) suggest that (XXXI) originates first from α,γ -diphenyl- $\Delta^{\beta,\gamma}$ -butenolide which isomerizes to α,γ -diphenyl- $\Delta^{\alpha,\beta}$ -butenolide; this upon exposure to air undergoes oxidative dimerization.



XXX



XXXI

In this work, heating α -phenyl- β -benzoylpropionic acid with acetic acid and sulfuric acid according to Baddar and Sherif (10) gave a solid m.p. 288-290° dec. in 83% yield. This material had many of the properties of Water's, and Yates and Clark's 288° oxidative dimer (XXXI) and will be considered to be the same as this material. It had infrared absorption at 5.70 μ and was too insoluble in ordinary solvents to obtain a molecular weight. The only solvents useful for recrystallization were boiling DMF or nitrobenzene, in which thermochromic behavior was noted. It was found that this substance would not undergo alkylation using several different procedures; a Grignard reaction also failed to have any effect on this material as previously noted. Its saponification with sodium hydroxide in diglyme for 17 hours gave a dark red solution, from which only a neutral product could be obtained, which after Norite treatment and several recrystallizations from benzene had m.p. 246-247° (clear melt). This 247° material had carbonyl absorption at 5.62 μ and a molecular weight value of 476 indicative of a $\Delta^{\beta\gamma}$ -butenolide dimer. Extending the saponification period of (XXXI) to 41 hours in ethylene glycol gave α -phenyl- β -benzoylpropionic acid (47%), the 247° dimer (14%) and acetophenone (approx. 2% determined by formation of the dinitrophenylhydrazone). A mixed melting point of this 247° dimer with the 288° oxidative dimer was depressed.

An attempt to resaponify the 247° dimer in ethylene glycol for 23.5 hours gave only recovered starting material. Apparently the α -phenyl- β -benzoylpropionic acid is formed by saponification of (XXXI) and does not arise from the 247° dimer under these conditions. The 247° dimer probably results from a rearrangement of (XXXI). Some evidence

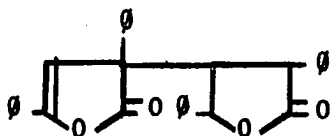
for the presence of free radicals was obtained in these saponifications of (XXXI) by observing color formation as the solutions were heated similar to that observed during the recrystallization of (XXXI). It is to be noted that none of the other workers have reported this 247° material from the saponification of the 288° dimer.

An NMR spectrum of this 247° dimer indicated the presence of 3 types of hydrogens, thereby excluding from consideration bislactones such as (XXX) or (XXXI). The peak at 5.90 τ (weak doublet) was assigned the β -hydrogen of the $\Delta^{\beta,\gamma}$ -butenolide ring and the γ -hydrogen of a butanolide ring. Peaks at 6.8 and 7.08 τ were assigned to the α and β hydrogen of the butanolide ring. The structure proposed for this dimer on the basis of the NMR and infrared spectra is (XXXII).

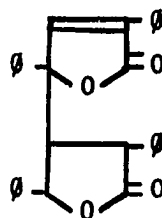
The previously described procedure of Yates and Clark (11) for the preparation of α,γ -diphenyl- $\Delta^{\alpha,\beta}$ -butenolide was found to give an oil, which was recrystallized from benzene in the presence of air to give a 77.5% yield of two high melting products. The previously mentioned oxidative dimer (XXXI) and a material m.p. 233.5-234.5° were present in a ratio of 1:2 (although another preparation, 71% yield, had this ratio reversed). The latter material had carbonyl absorption at 5.70 μ and gave molecular weight values of 482 and 498 together indicative of a $\Delta^{\alpha,\beta}$ -butenolide dimer. Both the 234.5° dimer and dimer (XXXII) had elemental analysis which indicated the formula $C_{32}H_{24}O_4$ indicating that this 234.5° dimer and dimer (XXXII) are isomers of each other. This new 234.5° dimer did not form a dinitrophenylhydrazone, and gave a depressed mixed melting point with both dimers (XXXI) and (XXXII). Saponification of this 234.5° dimer for 30 hours in diglyme gave an 86%

yield of α -phenyl- β -benzoylpropionic acid as well as a small amount of acetophenone (determined as the dinitrophenylhydrazone). In contrast to the oxidative dimer (XXXI) which does not undergo alkylation, the 234.5° dimer was easily alkylated.

The NMR spectrum of this 234.5° dimer had a peak at 4.47 τ which was assigned to the butanolide γ -hydrogen and a peak at 6.27 τ which was assigned to the α and β hydrogens of the butanolide ring. The β hydrogen of the butanolide ring appeared to be under the aromatic area. The Michael dimer (XXXIII) is proposed for this 234.5° material based on the NMR and infrared spectra.



XXXII



XXXIII

Along this same line, Ramirez and Rubin (7) reported the formation of a material m.p. 226-227° from α -methyl- β -benzoylpropionic acid, acetic anhydride and sulfuric acid which they describe as α -methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butanolide. In this work their procedure for preparation of the $\Delta^{\beta,\gamma}$ -isomer (by heating the keto acid with acetic anhydride) gave instead a 33% yield of the supposed " $\Delta^{\alpha,\beta}$ -isomer" with m.p. 229-230° dec. (continued recrystallization of this material raised the melting point to 232.5-233° dec.). This 233° material had carbonyl absorption at 5.68 μ and gave molecular weight values of 342 and 350 together indicative of a $\Delta^{\alpha,\beta}$ -butanolide dimer. Saponification of this material with potassium hydroxide for 2.5 hours gave an 86% yield

of α -methyl- β -benzoylpropionic acid. This material failed to undergo alkylation in several different attempts. A Grignard reaction on this material with phenylmagnesium bromide produced a white precipitate, but the material was recovered unchanged after the work up.

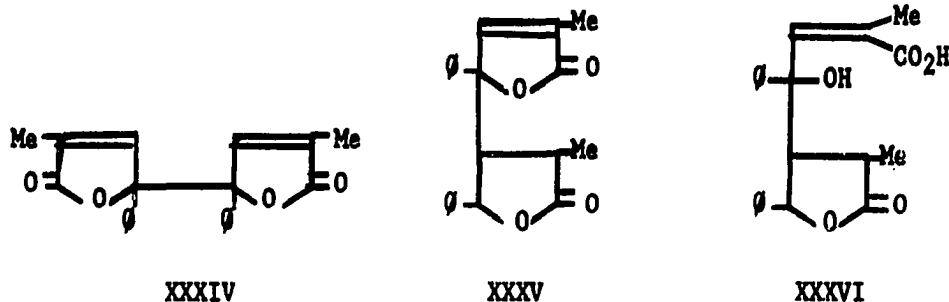
The NMR spectrum of this 233° dimer indicated only methyl and aromatic hydrogens in a ratio of 6:12. Apparently the β -hydrogens of the butenolide rings fall under the aromatic region. The failure of this material to alkylate and the infrared absorption would indicate a dimer similar to (XXXI). The oxidative dimer (XXXIV) is assigned to this 233° material.

A related substance was obtained from two different reactions on α -methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide, a butylation and an attempted benzylation, and had m.p. 179-179.5°. The diverse nature of these reactions indicate that this 179.5° material must be derived from the starting butenolide. This material had carbonyl absorption at 5.65 μ , and an elemental analysis and molecular weight value of 350 indicate that this substance was a dimer. Saponification of this product gave a lactone acid with carbonyl absorption at 5.61 and 5.86 μ , the first value is in agreement for a butanolid ring. Other values for seven saturated γ -lactones observed in this work were found over the range 5.61-5.75 μ . This indicates that probably both rings were saponified but that the γ -hydroxybutyric acid relactonized during the work up.

The NMR spectrum of the 179.5° material had a peak at 4.77 τ (doublet) assigned to the γ hydrogen of the butanolid ring, the butanolid methyl group was assigned to the 8.70 τ doublet, the butenolid methyl group was assigned to the 8.07 τ peak, the broad multiplet at

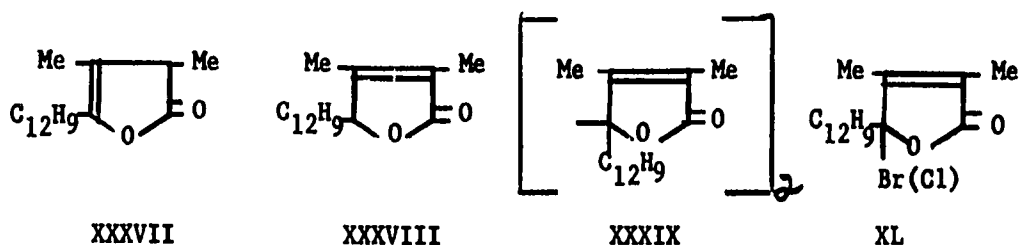
7-7.9 τ was assigned to the α and β hydrogens of the butanolide ring. The β hydrogen of the butanolide ring appeared to be under the aromatic area. The Michael dimer (XXXV) is proposed for this 179.5 $^\circ$ material based on the NMR and infrared spectra.

The NMR spectrum of the lactone acid gave only limited information due to low solubility. Other than the aromatic and methyl absorptions the only useful peak was found at 4.36 τ which was assigned to the β hydrogen of the unsaturated acid. However, a tentative assignment of (XXXVI) is proposed for this lactone acid on the basis of its formation from (XXXV).



In another case, Lutz and Couper (23) find that by proper choice of conditions, 3 compounds (XXXVII, XXXVIII, XXXIX) can be obtained from α,β -dimethyl- β -xenolacrylic acid. Both (XXXVII) and (XXXVIII) will give (XXXIX) when treated with Tollens reagent, but only (XXXVII) would give (XXXIX) when exposed to air. Some evidence was presented that a trace of sulfuric acid was necessary before the dimer would form from (XXXVII) and that even the presence of zinc dust and a nitrogen atmosphere would not prevent the formation of the dimer. During preparation of (XXXVII) using phosphoric acid in place of sulfuric acid, the dimer would not form even when air was bubbled through the solution. Treating (XXXVIII) with traces of sulfuric acid under the

same conditions did not produce any dimer. Evidence for the structure of (XXXIX) was obtained by coupling (XL) with copper-bronze to give the same material (m.p. 231-234° dec.) as obtained from (XXXVII).



This is the only example known which demonstrates which isomer is responsible for undergoing air oxidation. However, of all the $\Delta^{\alpha,\beta}$ -butenolides studied in this work only α,β,γ -triphenyl- $\Delta^{\alpha,\beta}$ -butenolide (described in Part I) and γ -methyl- $\Delta^{\alpha,\beta}$ -butenolide (XVIII) have been found to be stable in air. On the other hand none of the α,α -unsubstituted $\Delta^{\beta,\gamma}$ -butenolides have been found to be completely stable in air. For example, γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide (I) and the p-methoxy derivative both gave oily products after long periods of storage which cannot be attributed entirely to hydrolysis and may indicate some dimer formation due to a slow attack by oxygen. γ -Methyl- $\Delta^{\beta,\gamma}$ -butenolide (XV), while more stable than the others in this group, undergoes polymerization under the influence of ultraviolet light (24). In this work storage of α -angelica lactone (XV) in the dark for long periods produced some high boiling residue, which may indicate some dimer formation. The infrared spectrum of this residue indicated that only very small amounts of levulinic acid are present.

Available evidence indicates that this air oxidation occurs most readily with those compounds which have a favorable equilibrium set

up between the interconversion of the $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ -isomers. This interconversion is apparently relatively easy to establish only in those compounds which have γ as well as an α or β substituent, and an available α or γ hydrogen, with the exception of α,β,γ -triphenyl- $\Delta^{\alpha,\beta}$ -butenolide which is apparently a unique case (as shown by its reactions in Part I).

Whether or not air oxidations to other dimers proceed by way of the $\Delta^{\beta,\gamma}$ -isomers must await further experimental and mechanistic studies.

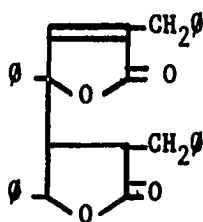
The formation of similar dimers under base catalyzed conditions (see dimer section in Part I) would require a different mechanism than the dimerization caused by air.

In this work formation of an oxidative dimer has also been observed under reduction conditions, for example, in the reduction of α -benzylidene- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide using a copper-zinc couple and acetic acid as in the procedure of Thiele and Mayr (8) a neutral material m.p. 218-219.5° was obtained in 12% yield along with a 14% yield of the desired monomeric α -benzyl- β -benzoylpropionic acid. A more effective copper-zinc couple (25) gave a 35% yield of the keto acid and only 0.6% of the dimer. This material is probably the same as the 212-215° material (described later) obtained by heating this keto acid with acetic anhydride. The possibility that this 219.5° material might have resulted from dimerization of the incompletely reduced α -benzyl- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide, which is the intermediate obtained by Thiele and Mayr in a similar reaction, after work up of the reaction mixture cannot be completely overlooked.

When α -benzyl- β -benzoylpropionic acid was heated with acetic anhydride an 11% yield of neutral material m.p. 212-215° was obtained. The infrared spectrum was identical (carbonyl absorption at 5.66 μ) to that of the 219.5° material described above in the copper-zinc couple reaction. Due to the small amount of material available it was not examined further.

An entirely different approach to obtain α -benzyl- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide led to a different dimer. For example, Mark (26)⁷ reported that lithium aluminum hydride reduction of α -benzylidene- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide gave a substance m.p. 161-162° and was assumed by her to be α -benzyl- γ -phenyl- $\Delta^{\alpha\beta}$ -butenolide. Thiele and Mayr (8), however, reported that the $\Delta^{\beta\gamma}$ -isomer of this butenolide melted at 100-101° and that the $\Delta^{\alpha\beta}$ -isomer melted at 67°. In this work, use of her procedure gave a compound m.p. 160-161° which had the properties reported by her but which gave molecular weight values of 495 and 498 indicating that this substance is actually a dimer. The presence of carbonyl absorption at 5.59 and 5.67 μ (in KBr; in chloroform only carbonyl absorption at 5.65 μ is observed) and the relatively low melting point indicate that this material is not an oxidative dimer. Saponification of this dimer for 48 hours gave a 98.5% yield of α -benzyl- β -benzoylpropionic acid. Benzylation of this dimer with benzyl chloride and sodium hydride gave a 55% yield of α,α -dibenzyl- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (II). Hydrogenation of this dimer with Pt/C at 46 p.s.i. for 15 hours had no effect, the dimer being recovered unchanged, while Pd/C at 46 p.s.i. for 17.5 hours gave a 90% yield of neutral material which had m.p. 193-193.5°. Carbonyl absorption, an analysis and the molecular weight all indicate the saturated form of the dimer.

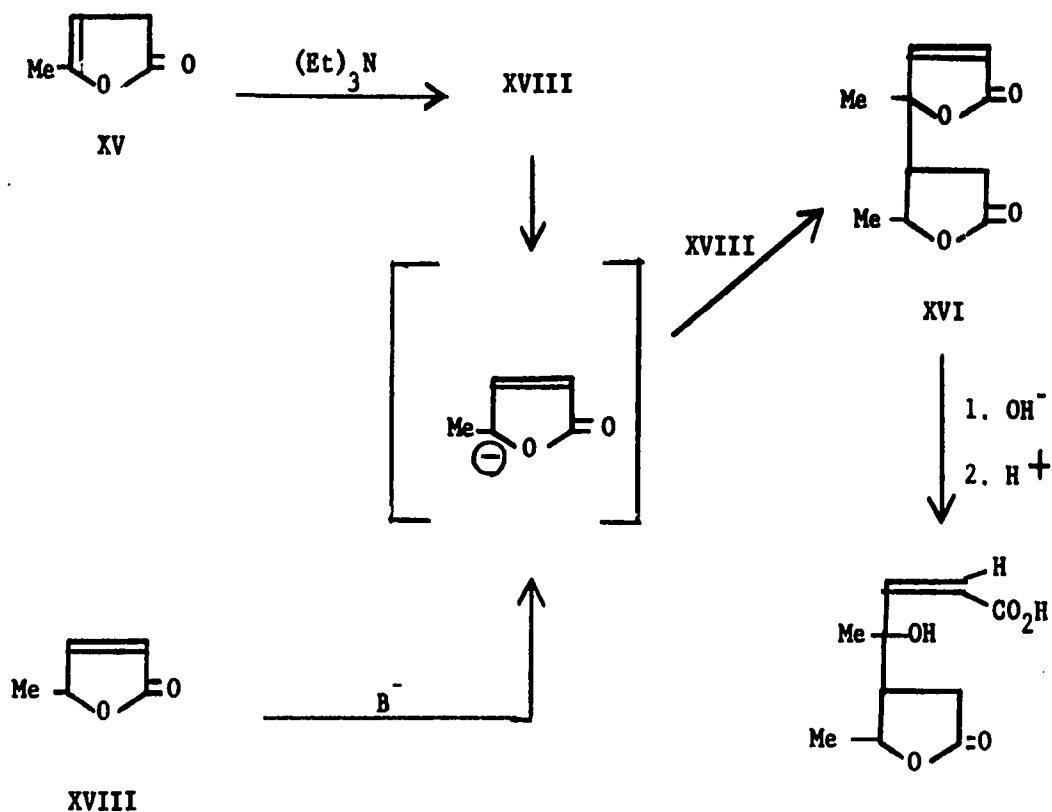
The NMR spectrum of this 161° dimer indicated the presence of 28 hydrogen atoms assigned for the nonaromatic hydrogens as follows: broad peak at 7.15 τ assigned to the 2 hydrogens of the butanolide benzyl group and the α and β hydrogens of the butanolide ring, a sharp singlet at 6.49 τ assigned to the benzyl hydrogens of the butanolide ring, a doublet at 4.79 τ assigned to the γ hydrogen of the butanolide ring, and a broad peak at 3.70 τ assigned to the β hydrogen of the butanolide ring. On the basis of the NMR and infrared spectra the structure assigned to this 161° dimer is the Michael dimer (XLI).



XLI

The isomerization of α -angelica lactone (XV) to β -angelica lactone (XVIII) is known to occur under the influence of mild basic catalysts such as triethylamine (27). Syhora (28) has recently reported that a Michael dimerization can also occur during this isomerization with triethylamine to give (XVI). He suggested that the dimerization occurred by way of β -angelica lactone. He reported the transformations shown at the top of the following page.

This dimerization to (XVI) was confirmed independently, in this work, during an attempt to isomerize α -angelica lactone to β -angelica lactone using triethylamine. A 75% yield of an oily high boiling liquid was obtained. This oil crystallized after standing several months. While no suitable solvent was found for recrystallization,



washing with benzene-hexane gave a solid m.p. $73-83^\circ$ (the reported melting point is $85-85.5^\circ$ (28)). Syhora reported that (XVI) had infrared absorption at 5.63μ , whereas, in this work a broad band at $5.6-5.75\mu$ was observed. Additional evidence for the dimeric nature of this material was obtained from the molecular weight determination. This material also failed to give a dinitrophenylhydrazone. In contrast, α -angelica lactone gave the dinitrophenylhydrazone of levulinic acid within 30 seconds using Shine's reagent (9), whereas, β -angelica lactone gave only a brownish coloration but no precipitate after 5 minutes under the same conditions. Ramirez and Rubin (7) also found that a $\Delta^{\beta\gamma}$ -butenolide forms a dinitrophenylhydrazone derivative, whereas, the corresponding $\Delta^{\alpha\beta}$ -isomer (which was in reality probably a $\Delta^{\alpha\beta}$ -butenolide dimer, XXXIV) fails to form a derivative.

This Michael dimer (XVI) was also found to undergo benzylation to give α,α -dibenzyl- γ -methyl- $\Delta^{\alpha,\gamma}$ -butenolide (XVII).

Conclusive evidence for the structure of this dimer (XVI) was obtained from the NMR spectrum. The characteristic hydrogen absorption for the α and β hydrogens of the butenolide ring were found at 3.88 and 2.50 τ respectively (doublets for each), the γ hydrogen of the butenolide ring was found at 5.62 τ (quintuplet), the α and β hydrogens of the butenolide ring were found at 7.32 τ (rough triplet).

Acylation Reactions

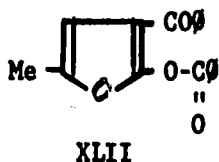
It has been observed by other workers that the more reactive alkylating agents would undergo reaction with the solvents DMSO or DMF (29,30,31,32). This difficulty is a more serious limitation when acylations are attempted using acyl halides. It has been reported that acyl halides and DMSO mixtures can result in violent reactions (30). The reaction of acyl halides with DMF has been reported to be competitive with the reaction of the acyl halide and the anionic substrate (31,32) resulting in low to moderate yields of the acyl derivatives of esters and mercaptals.

The acylation reactions of α -angelica lactone discussed below are summarized in Table III, reactions 5-7.

Reaction of α -angelica lactone (XV) with benzoyl chloride and sodium hydride in DMF (Table III, reaction 5 and 6) gave a yellow product, the molecular weight and elemental analysis of which indicate that two benzoyl groups had been introduced. This material had carbonyl absorption at 5.65 and 5.72 μ .

The NMR spectrum of this compound was quite conclusive and

showed the typical ortho hydrogen absorption of benzoate esters at 1.82 τ (weak doublet), a sharp peak at 3.91 τ assigned to the 4-hydrogen of the furan ring, and a peak at 7.88 τ assigned to hydrogens of the 5-methyl group of the furan ring. On the basis of the NMR and infrared spectrum, structure (XLII) is assigned to this acyl derivative.



Reaction of α -angelica lactone with methyl benzoate and sodium hydride in DMSO (Table III, reaction 7) did not produce this furan derivative (XLII), but instead, a low yield of oil was obtained by chromatography which had infrared absorption at 5.85 μ and also indicated the presence of aromatic absorption peaks. Saponification of this uncharacterized material gave a dark oil from which only acetophenone could be obtained (determined by dinitrophenylhydrazone derivative).

On the other hand an attempt to acylate α -methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide with methyl benzoate and sodium hydride in DMSO gave only the Michael dimer (XXXV) which has already been described in the dimer section.

In view of the difficulty of finding the proper solvent and acylating agent, consistent with reasonable product yields, these reactions were not explored further. The modest yield of the acyl product from α -angelica lactone and the acylation reaction reported in Part I, indicate that acylations of butenolides are feasible. A more complete study of these acylations must await the solution of the reaction conditions problem.

Hydrogenation Studies

In general, it has been found that hydrogenations of butenolides using palladium on charcoal result in hydrogenation with hydrogenolysis of the benzyl position with overall absorption of 2 moles of hydrogen, as indicated in the following examples.

Hydrogenation of α,α -dibenzyl- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (II) with Pd/C, has already been described in connection with the proof of structure of this compound, gave a 96.5% yield of α,α -dibenzyl- γ -phenylbutyric acid (III).

Hydrogenation of γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (I) with Pd/C in ethyl acetate under 45 p.s.i. for 16 hours gave a 90% yield of γ -phenylbutyric acid (VI).

Attempted hydrogenation of the Michael dimer (XLI) with Pd/C at atmospheric pressure resulted in no reaction after 6 hours. However, under 46 p.s.i. for 17.5 hours in ethyl acetate a 90% yield of material m.p. 192.5-193.5° was obtained which had a molecular weight value of 508 and carbonyl absorption at 5.69 μ . No acid was obtained from this reaction, indicating that with this dimer hydrogenolysis had not occurred. This is further indication of the tertiary nature of the butenolide ring γ -position (benzyl carbon) in (XLI). This material is apparently the saturated form of the dimer (expected mol. wt. 503).

Jacobs and Scott (33,34) have shown that with Adams catalyst, the $\Delta^{\beta\gamma}$ -butenolides are reduced to a mixture of butenolide and the corresponding substituted butyric acid in a ratio of approximately 4:1, although the more lightly substituted compounds often gave only the butyric acid. On the other hand the $\Delta^{\alpha\beta}$ -butenolides under the same

conditions would give only the butanolide, providing that the butenolide would not isomerize during the reaction. If isomerization could occur in the compound the result was again a mixture of butanolide and butyric acid but the ratio was not approximately 7:1. A butanolide was found not to undergo hydrogenolysis under these same conditions, which indicates that the hydrogenolysis occurs before or at the same time that the double bond is reduced.

In this work reductions were carried out mostly with platinum on charcoal in ethyl acetate with the following results.

Hydrogenation of α,α -dibenzyl- γ -methyl- $\Delta^{\beta\gamma}$ -butenolide (XVII), which has already been described in connection with the proof of structure of this compound, gave an 83.5% yield of α,α -dibenzyl- γ -methylbutanolide (XXII) and a 14% yield of α,α -dibenzylvaleric acid (XXIII) (ratio 6:1).

Hydrogenation of α,α -dibenzyl- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (II) at 46 p.s.i. for 6 hours, gave a 62% yield of α,α -dibenzyl- γ -phenylbutanolide (VII) and a 30% yield of α,α -dibenzyl- γ -phenylbutyric acid (III) (ratio 2:1).

Hydrogenation of γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (I) at 45 p.s.i. for 3 hours, gave a 6% yield of γ -phenylbutanolide (VIII) and a 79.5% yield of γ -phenylbutyric acid (VI) (ratio 1:13).

Attempted hydrogenation of the Michael dimer (XLI) at 47 p.s.i. for 15 hours, gave no reaction.

PART II

EXPERIMENTAL

All melting points and boiling points are uncorrected. The reaction solvents ether, benzene and toluene were dried over sodium wire. Diglyme was distilled to remove water prior to use. Dimethyl sulfoxide and dimethylformamide were dried over calcium hydride at 100° and distilled from calcium hydride under reduced pressure. In some cases the distillate was further dried by passage through a 4 foot column of 4A molecular sieve (Linde). The term "worked up in the usual way", unless otherwise described, for a basic aqueous phase means that the solution was acidified with hydrochloric acid, extracted several times with benzene, the combined benzene extracts washed with water, the benzene solution dried over sodium sulfate, and the solution concentrated. Unless otherwise indicated commercial sodium hydride (powdered under a nitrogen atmosphere in a dry box) was used. Molecular weight determinations were performed in benzene using a Mechrolab vapor pressure osmometer. Infrared spectra were recorded by a Perkin-Elmer Model 21 spectrophotometer and nuclear magnetic resonance spectra by a Varian A-60 spectrometer.

γ -Phenyl- $\Delta^{\beta\gamma}$ -butenolide (I). β -Benzoylpropionic acid (35) (100 g., 0.55 mole, recrystallized from benzene, m.p. 115.5-116°) was placed in a 500 ml. glass-stoppered Erlenmeyer flask containing 200 ml.

of acetic anhydride and 5 drops of concentrated sulfuric acid. The mixture was warmed on a steam bath until solution was complete, and allowed to stand for 3 days at room temperature. The solution was saturated with hexane, and cooled in a refrigerator. There was obtained 64.5 g. (72%) of the product as light orange plates m.p. 90-92°. Recrystallization from hexane gave 61 g. of light yellow plates, m.p. 91-92.5°; literature (2) value, m.p. 92-93°. The solvents were removed from the mother liquor under reduced pressure and the dark red residue was extracted with hot hexane to give an additional 13 g. (14.5%) of less pure red colored product, m.p. 88-90°.

γ -(p-Methoxyphenyl)- $\Delta^{\beta\gamma}$ -butenolide. The procedure of El-Assel and Shehab (5) was used. β -(p-Anisoyl)propionic acid (10 g., 0.0481 mole) and 20 ml. of acetic anhydride was heated on a steam bath until solution occurred, kept at 55° for 5 hours and then left at room temperature overnight. The crystalline mass was filtered and washed with hexane. There was obtained 6.33 g. of product m.p. 108.5-111° as salmon pink crystals. The mother liquor upon cooling gave an additional 1.85 g. of red colored product m.p. 107-110°. The total crude yield amounted to 89.5%. Extraction of the crude product with hot hexane removed most of the red colored impurity which was left behind. However, even Norite treatment does not give a completely colorless product. These procedures result in only small losses and give a yellowish-orange product with m.p. 110-111°. The recorded value is m.p. 110-111° (5).

γ -Methyl- $\Delta^{\beta\gamma}$ -butenolide (XV). The procedure of Helberger, Ulubay, and Civelekoglu (12) was used. One hundred grams (0.862 mole) of levulinic acid (commercial sample from Quaker Oats) and one gram of

85% phosphoric acid was subjected to slow distillation for 16 hours at 18 mm. The distillate was washed with dilute sodium carbonate and 2 portions of water, dried over sodium sulfate and fractionated under reduced pressure. α -Angelica lactone (XV), 57 g., m.p. 19.5° , b.p. $66-67^{\circ}$ at 18 mm., n_D^{25} 1.4448, was obtained in 67.5% yield. The recorded constants (36) are m.p. 18° , b.p. 53° at 12 mm., and $n_D^{20.4}$ 1.4476. With Shine's reagent (9) diluted (1:1) with water, (XV) gave a dinitrophenylhydrazone of levulinic acid within 30 seconds, m.p. $205-206^{\circ}$ (dec.) from ethanol.

α -Methyl- β -phenyl- $\Delta^{\alpha\beta}$ -butenolide (IX). Into a 50 ml. Erlenmeyer flask was placed 4.42 g. (0.023 mole) of α -methyl- β -benzoylpropionic acid and 20 ml. of acetic anhydride. Air was displaced from the flask through an adaptor which introduced dry, oxygen-free nitrogen through an inlet tube which extended almost to the surface of the liquid and with an exit tube at the very top of the adaptor to insure that no trapped air remained. A minimum of 900 ml. of nitrogen was used to sweep the flask, after which a flow rate of approximately one milliliter per minute was used while heating the mixture on a steam bath for 5 hours. The solvent was removed in vacuo over a 5 hour period to give a quantitative yield of light yellow oil, which would not crystallize on standing in vacuo. The crude (IX) had infrared absorption (neat) at 5.68μ ($\Delta^{\alpha\beta}$ -butenolide carbonyl). Molecular weight determinations on freshly prepared material indicated that the product was essentially free of dimer; however, after short exposure to air (approx. 5 hours) a crystalline dimer started to separate which had m.p. $225-226^{\circ}$ dec.

No further attempts were made to purify this oil in view of the relative ease of its conversion to the dimer. However, if during the removal of the excess acetic anhydride, heat from a small flame was played on the bottom of the flask the product could be flash distilled. This flash distilled oil also would not crystallize. The infrared spectra of the flash distilled and crude product were practically identical, indicating that little advantage was to be gained using this distilled product.

In one preparation of (IX), evidence was obtained for the presence of some of the $\Delta^{\beta\gamma}$ -isomer, indicated by a shoulder on the carbonyl absorption peak at 5.55μ .

α,γ -Diphenyl- $\Delta^{\alpha,\beta}$ -butenolide. α -Phenyl- β -benzoylpropionic acid (2.54 g., 0.01 mole) and 7 ml. of acetic anhydride were treated exactly as described for the preparation of α -methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide, except that the solution was heated for 15 hours, and the solvent was removed in vacuo over a 36 hour period. A quantitative yield of colorless waxy solid was obtained. This material had infrared absorption in chloroform at 5.70μ (carbonyl). A molecular weight determination after a short exposure to air indicated that one half of the product had dimerized. Attempts to recrystallize the crude product gave only a dimer m.p. $225-233^{\circ}$ (XXXIII). No further attempts at purification were attempted.

α -Benzyl- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (XII). α -Benzyl- β -benzoyl propionic acid (prepared according to the procedure of Thiele and Mayr (8)) (2.68 g., 0.01 mole) and 11 ml. of acetic anhydride were treated using the same conditions as described for the preparation of

α -methyl- γ -phenyl- $\Delta^{\alpha\beta}$ -butenolide. A quantitative yield of crude solid was obtained. The crude (XII) had infrared absorption in chloroform at 5.57μ ; a shoulder at 5.67μ indicated the presence of some of the $\Delta^{\alpha\beta}$ -isomer. A sample of this crude product was recrystallized from benzene-hexane and had m.p. $100-101^\circ$. The recorded value is m.p. $100-101^\circ$ for this labile form (8). Another recrystallization, this time from methanol, resulted in the formation of a dimer m.p. 195° dec.

α,α -Dibenzyl- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (II). Method A.

To a stirred and refluxing mixture of 12.6 g. (0.262 mole) of 50% sodium hydride in oil and 280 ml. of dry toluene was added a solution of 20 g. (0.125 mole) of γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (I), and 31.7 g. (0.25 mole) of benzyl chloride, in 170 ml. of dry toluene over a 45 minute period. The mixture was refluxed for an additional 3 hours until evolution of hydrogen had ceased. The brownish-red solution was cooled, filtered, extracted with water, and dried over sodium sulfate. Cooling the solution in the refrigerator afforded 9.4 g. of fluffy white crystals, m.p. $174.5-175.5^\circ$, and a further 7.4 g. (m.p. $172-173.5^\circ$) was obtained on concentrating the solution. The mother liquor was flooded with hexane to give 9.21 g. of a tan powder which was extracted with hexane in a Soxhlet extractor to give, when recrystallized from toluene 1.9 g. of (II), m.p. $172-174^\circ$. The total crude yield of (II) was 18.7 g. (44%). An analytical sample from a previous preparation was recrystallized from toluene, m.p. $175.5-176^\circ$. The product (II) had infrared absorption at 5.55μ (CHCl_3); 5.60μ (KBr).

Anal. Calcd. for $\text{C}_{24}\text{H}_{20}\text{O}_2$: C, 84.68; H, 5.92; mol. wt., 340.

Found: C, 84.47; H, 6.20; mol. wt., 339.

Method B. Attempted Monobenylation of γ -Phenyl- $\Delta^{B,\gamma}$ -butenolide. A mixture of 10 g. (0.063 mole) of γ -phenyl- $\Delta^{B,\gamma}$ -butenolide, and 1.58 g. (0.066 mole) of sodium hydride (from sodium hydride in oil after extracting the oil with benzene), in 100 ml. of diglyme was heated to reflux with stirring for 15 minutes. A solution of 7.9 g. (0.062 mole) of benzyl chloride and 20 ml. of diglyme was added over a 15 minute period. The mixture was refluxed for an additional 3.5 hours. The diglyme was removed under reduced pressure. The residue was taken up in benzene, extracted with water, dried over sodium sulfate, concentrated and diluted with hexane. The only crystalline material that was obtained was 1.38 g. of α,α -dibenzyl- γ -phenyl- $\Delta^{B,\gamma}$ -butenolide (6.5%) m.p. 152-167°. Recrystallization of this material from benzene raised the melting point to 176-176.5°.

Method C. From Benzylation of Michael Dimer (XLI). To a stirred and refluxing mixture of 0.32 g. (0.013 mole) of sodium hydride, 1.52 g. (0.012 mole) of benzyl chloride, and 60 ml. of dry toluene was added a slurry of 3 g. (0.012 mole) of dimer (XLI) in 80 ml. of dry toluene, over a 25 minute period. The mixture was refluxed for an additional 2.5 hours. After cooling the reaction mixture, the solution was filtered, washed with water, dried over sodium sulfate, and evaporated to dryness. There was obtained 3.53 g. of crude butenolide (II) in 86.5% yield. Recrystallization from benzene gave 2.24 g. (55%) of colorless fluffy crystals, m.p. 176-176.5°. A mixed melting point with the previously described material was not depressed.

α,α -Dimethyl- γ -phenyl- $\Delta^{B,\gamma}$ -butenolide (X). A mixture of sodium hydride (0.53 g., 0.022 mole) and 25 ml. of dry dimethyl

sulfoxide was stirred magnetically under a nitrogen atmosphere while a solution of 3.48 g. (0.02 mole) of α -methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide in 10 ml. of benzene was added dropwise (10 drops) to start the reaction. An immediate yellow-green color was obtained. Methyl iodide 5 g. (0.035 mole) was added to the addition funnel and the rest of the mixture was added dropwise over a 50 minute period. A slight warming of the flask contents was observed, at the start of the reaction, accompanied by refluxing of the methyl iodide. An additional 5 g. of methyl iodide was added and the reaction mixture stirred for an additional 40 minutes until hydrogen evolution had ceased.

The reaction mixture was poured into 500 ml. of water and extracted with benzene. The aqueous phase after the usual work up afforded 0.04 g. (1%) of the thick oily pseudo acid α,α -dimethyl- γ -phenyl- γ -hydroxybutanolide indicated by infrared absorption at 3.0μ (hydroxyl), 5.68μ (carbonyl) and lack of absorption in the region 6.1μ indicating absence of carbon-carbon double bond. Due to lack of material this pseudo acid was not examined further.

The organic phase gave 3.85 g. of crude oil, of which 3.76 g. was chromatographed on 100 g. of 100/200 mesh Florisil using benzene as the eluant. The first 75 ml. gave 0.02 g., which did not show carbonyl absorption and was discarded. The next 50 ml. gave 0.72 g. of (X), carbonyl absorption (neat) 5.55μ . The next 50 ml. gave 0.66 g. of a mixture of (X) and an uncharacterized oil which was estimated from the infrared spectrum to contain approximately 0.16 g. of (X). The total crude yield of (X) both isolated and estimated was approximately 24%. Continued elution of the column with chloroform-benzene (300 ml., 1:1

mixture) afforded 1.24 g. of crude oxidative dimer (XXXIV) in 36% yield. A recrystallized sample of this dimer had m.p. 233-234° dec. Continued elution with methanol gave only an uncharacterized oil.

The 0.72 g. of (X) obtained above could not initially be induced to crystallize, but after standing 7 days a solid keto acid (total amount 0.56 g.) m.p. 169-173° was obtained. Recrystallization of a sample of this acid from ethanol raised the melting point to 175.5-176.5°.

An analytical sample of this acid was obtained from another alkylation reaction of γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (X) using sodium hydride and dimethyl sulfate. The reaction required 3.5 hours for completion. α,α -Dimethyl- β -benzoylpropionic acid (V) was obtained in 20% yield, m.p. 173.5-174°. A mixed melting point with the above acid was not depressed.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; mol. wt., 206.

Found: C, 69.80; H, 7.03; neu. eq., 207.

A dinitrophenylhydrazone of this keto acid (m.p. 202-203°) was obtained using Shine's reagent (9). The literature value (4) is m.p. 173° for the keto acid and 198-199° for the dinitrophenylhydrazone.

α,α -Dibenzyl- γ -(p-methoxyphenyl)- $\Delta^{\beta\gamma}$ -butenolide. One gram (0.0053 mole) of γ -(p-methoxyphenyl)- $\Delta^{\beta\gamma}$ -butenolide was added all at once with stirring to a mixture of sodium hydride (0.6 g., 0.025 mole), benzyl chloride (1.34 g., 0.016 mole) and 50 ml. of dry dimethyl sulfoxide at room temperature. An immediate green color formed and the initial evolution of hydrogen appeared to be over after stirring for 30 minutes. Stirring was continued for an additional 75 minutes after

which the solution was a brownish color. The reaction mixture was filtered and the filtrate was poured into 1.2 l. of water, acidified and extracted with ether. The ether and some unreacted benzyl chloride was removed in vacuo and the residue (2.14 g.) was recrystallized from benzene-hexane. There were obtained 2 crops of impure dibenzyl product (0.44 g.). The residue from the recrystallization was chromatographed on 10 g. of alumina using benzene. Concentration of the effluent gave an additional 3 crops of the product (total amount 0.36 g.). The total crude yield of the product 0.76 g. (39%) was recrystallized from benzene-hexane (Norite) to give 0.59 g. (30%) of the dibenzyl butenolide m.p. 144-148°. An analytical sample, from methanol, was obtained from a previous reaction and had m.p. 148-148.5°, infrared absorption (CHCl₃), 5.57 μ .

Anal. Calcd. for C₂₅H₂₂O₃: C, 81.05; H, 5.99; -OCH₃, 8.38.

Found: C, 81.26; H, 5.89; -OCH₃, 8.67.

α -Methyl- α -benzyl- δ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide (XI). From α -Methyl- δ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide. A mixture of sodium hydride (0.5 g., 0.208 mole), benzyl chloride (0.59 g., 0.0047 mole) and 40 ml. of dry dimethyl sulfoxide was stirred at room temperature under a nitrogen atmosphere, while the butenolide (IX) (0.81 g., 0.0047 mole) was added in 5 ml. of benzene. A cloudy yellow color formed and after stirring for one hour (the reaction appeared to be over within 25 minutes) a clear straw colored solution resulted. The excess sodium hydride and some sodium chloride was filtered off and the filtrate was poured into 900 ml. of water and extracted with ether. The usual work up and recrystallization from benzene-hexane afforded 0.64 g. of (XI) m.p.

123.5-131° (52% yield). Two recrystallizations from benzene and one from methanol gave an analytical sample m.p. 132-132.5°, infrared absorption (KBr), 5.58 μ .

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10; mol. wt., 264.

Found: C, 81.64; H, 6.06; mol. wt., 260.

From α -benzyl- δ -phenyl- $\Delta^{2,3}$ -butenolide. A mixture of sodium hydride (0.24 g., 0.01 mole) and 25 ml. of dry dimethyl sulfoxide was stirred magnetically under a nitrogen atmosphere. Part of a solution of the butenolide (XII) (2 g., 0.008 mole) in 10 ml. of dimethyl sulfoxide and 10 ml. of benzene was added to initiate the reaction; the rest of the solution together with methyl iodide (5 g., 0.055 mole) was then added over a 15 minute period. The lemon-yellow color slowly faded after stirring for an additional 2 hours. A maximum temperature of 32° (6° rise) was attained. The excess sodium hydride was filtered, the filtrate poured into 500 ml. of water, and the neutral solution extracted with benzene. The usual work up and recrystallization from benzene-hexane afforded 1.57 g. of (XI) m.p. 126-131° (74.5% yield). A recrystallization from methanol (Norita) gave 1.12 g. (53%) of (XI) m.p. 132-133°. Its infrared spectrum was identical to the above material and a mixed melting point was not depressed.

α -Methyl- α -butyl- δ -phenyl- $\Delta^{2,3}$ -butenolide (XIII). A mixture of sodium hydride (0.5 g., 0.021 mole) and 25 ml. of dry dimethyl sulfoxide was stirred magnetically under a nitrogen atmosphere. Ten drops of a solution of α -methyl- δ -phenyl- $\Delta^{2,3}$ -butenolide (IX) (1.74 g., 0.01 mole) in 5 ml. of benzene was added to initiate the reaction. An immediate yellow-green color was obtained. The rest of the butenolide

solution and n-butyl bromide (1.5 g., 0.011 mole, dried over CaH_2) was added dropwise, and stirring was continued for 3 hours. A moderate evolution of hydrogen and warming of the flask contents was observed. The olive green reaction mixture was filtered to remove an insoluble solid which gave a strong bromide ion test. The reaction mixture was poured into 500 ml. of water and the slightly basic solution was extracted with benzene. The organic phase after concentrating and chromatographing on 33 g. of alumina, gave 0.9 g. of pure (XIII) as a thick oil (39% yield). This chromatographed material was identical (infrared spectrum) to the low melting analytical sample obtained in a previous reaction which had m.p. $33-34^\circ$. This analytical sample had infrared absorption (neat), strong carbon-hydrogen stretching vibrations 3.41μ , shoulder at 3.28 and 3.50μ and carbonyl absorption at 5.57μ .

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_2$: C, 78.23; H, 7.88.

Found: C, 78.44; H, 7.78.

The aqueous phase after work up and recrystallization from benzene-hexane, gave a 12% yield of α -methyl- α -butyl- β -benzoylpropionic acid (XIV), m.p. $108-112^\circ$. This keto acid had an infrared spectrum identical with that obtained by intentional saponification of butenolide (XIII) (see next section).

α -Methyl- α -butyl- β -benzoylpropionic acid (XIV). α -Methyl- α -butyl- γ -phenyl- ~~β~~ -butenolide (XIII) (0.89 g.) was saponified for 17.5 hours with 20 ml. of 10% sodium hydroxide and 5 ml. of ethanol. The usual work up gave 0.8 g. (83% yield) of keto acid (XIV), m.p. $101-106^\circ$. Two recrystallizations from benzene-hexane gave an analytical sample, m.p. $111-111.5^\circ$, infrared absorption (KBr), 5.94μ .

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; mol. wt., 248.

Found: C, 72.29; H, 8.02; neu. eq., 247.

The 2,4-dinitrophenylhydrazone of this keto acid was prepared using Shine's procedure (9). The derivative, after recrystallization from ethanol, melted at 164.5-165°.

Anal. Calcd. for $C_{21}H_{24}O_6N_4$: C, 58.87; H, 5.65; N, 13.08.

Found: C, 58.64; H, 5.82; N, 13.10.

α,δ -Diphenyl- α -benzyl- $\Delta^{\alpha,\delta}$ -butenolide. From α,δ -Diphenyl- $\Delta^{\alpha,\beta}$ -butenolide. A mixture of sodium hydride (0.3 g., 0.0125 mole) and 15 ml. of dry dimethyl sulfoxide was stirred magnetically under a nitrogen atmosphere. A few drops of a solution of α,δ -diphenyl- $\Delta^{\alpha,\beta}$ -butenolide (2 g., 0.0085 mole) in 20 ml. of dimethyl sulfoxide and 10 ml. of benzene was added to initiate the reaction. An immediate green color was formed. The rest of the butenolide solution and 1.27 g. (0.01 mole) of benzyl chloride was added dropwise over a 20 minute period. A moderate evolution of hydrogen was observed in addition to warming of the flask contents. Stirring was continued for an additional 1.5 hours during which the then gold colored solution turned orange. The reaction mixture was filtered (the precipitate gave a strong chloride ion test) the filtrate was poured into 500 ml. of water and the neutral mixture was extracted with benzene. The organic phase was worked up in the usual way and the solvent evaporated. The residue was recrystallized from benzene-methanol. A precipitate remained (approx. 5 mg.) m.p. 290° dec. (infrared spectrum was identical to the oxidative dimer XXXI). Three crops of the (dimer free) butenolide product were obtained from the benzene-methanol solution; the

total yield of the product was 2.15 g. (77.5%) m.p. 152-161°. A sample of this product was chromatographed on alumina and recrystallized twice from benzene to give an analytical sample m.p. 155-155.5°, infrared absorption (KBr), 5.60 μ .

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56; mol. wt., 326.

Found: C, 84.71; H, 5.50; mol. wt., 323.

The solvent free residue from the initial recrystallizations was chromatographed on alumina. No additional benzyl butenolide product was obtained. However, extracting the alumina with dilute sodium carbonate solution afforded an acid (0.52 g., m.p. 150.5-151°) from benzene-hexane. It showed a depressed mixed melting point with α -phenyl- β -benzoylpropionic acid, but a mixed melting point with α -benzyl- α -phenyl- β -benzoylpropionic acid (m.p. 150-151°) described below was not depressed. This 0.52 g. of keto acid represents an 18% yield.

From Michael Dimer (XXXIII). The reaction of 2 g. (0.0042 mole) of Michael dimer (XXXIII) with sodium hydride (0.3 g., 0.0125 mole) and benzyl chloride (1.08 g., 0.0085 mole) in 35 ml. of dimethyl sulfoxide and 10 ml. of benzene, under the same conditions as described above for the monomer, required 1.75 hours for completion. The usual work up gave, 1.76 g. of the product (64%) m.p. 152-155°, from the organic phase. The aqueous phase gave, after recrystallization from benzene-hexane, 0.44 g. (15%) of the low melting (m.p. 124-126°) α -benzyl- α -phenyl- β -benzoylpropionic acid described below.

α -Benzyl- α -phenyl- β -benzoylpropionic acid. Saponification of 0.3 g. of α, γ -diphenyl- α -benzyl- $\Delta^{\beta\gamma}$ -butenolide with 30 ml. of 5% sodium hydroxide and 4 ml. of ethanol for 53 hours at reflux

temperature, gave a quantitative yield of the crude acid. Recrystallization of the crude acid from benzene-hexane gave a solid with strange melting behavior. A preheated melting point bath caused some initial melting at 108° , resolidification occurred at about 120° and with continued heating remelting occurred at $146-148^{\circ}$. Starting with a cold bath the melting point was $149-150.5^{\circ}$. Recrystallization of this material (0.31 g.) from methanol-hexane gave a material m.p. $124-125.5^{\circ}$. Continued heating of this material does not cause it to solidify. However, heating a sample of this material in an oven at 108° for 5 days changes the melting point to softening at 130° , m.p. $150-151^{\circ}$. A preheated bath gives the melting and resolidification behavior as first noted.

Infrared spectra (KBr) of both the 125.5 and 151° material were identical, carbonyl 5.90μ . The NMR (CDCl_3), τ values for the 125.5° acid; -1 (broad singlet, 1H); 2.08 (center of weak doublet, 2H); 2.68 (center of multiplet, 13H); 6.37 (singlet, 4H).

The 125.5° acid is not an alcoholate, since this same melting point was observed (by recrystallization from benzene-hexane) from acid obtained by an accidental hydrolysis during preparation of the parent butenolide. Apparently these are different crystal modifications, easily transformed by heat.

Anal. Calcd. for $\text{C}_{23}\text{H}_{20}\text{O}_3$: C, 80.21; H, 5.85; mol. wt., 344.

Found for 125.5° acid: C, 80.23; H, 5.64; neu. eq., 347.

Found for 151° acid: C, 80.58; H, 5.88; neu. eq., 343.

α,γ -Diphenyl- α -cyclopentyl- $\Delta^{\beta\gamma}$ -butenolide. A mixture of sodium hydride (0.3 g., 0.0125 mole) and 25 ml. of dry dimethyl sulfoxide

was stirred magnetically under a nitrogen atmosphere at room temperature. A slurry of 2 g. (0.0042 mole) of the Michael dimer (XXXIII) in 10 ml. of dimethyl sulfoxide and 8 ml. of benzene was added dropwise over a 15 minute period. A lime green color formed initially, but by the end of the addition of the dimer the solution had turned brownish-yellow. To this solution was added cyclopentyl bromide (1.27 g., 0.00852 mole, dried over CaH_2) in 5 ml. of benzene with continued stirring for 2 more hours. The solution was filtered (the precipitate gave a strong bromide ion test), the filtrate poured into 500 ml. of water, and the slightly basic mixture extracted with benzene. Work up of the organic phase in the usual way gave, from benzene, 1.21 g. (47%) of the product m.p. $116-118.5^\circ$. Two recrystallizations from methanol gave an analytical sample (0.98 g., 38%) m.p. $119-120^\circ$, infrared absorption (KBr) strong (CH_2) 3.36μ shoulder at 3.47μ and carbonyl at 5.60μ .

Anal. Calcd. for $\text{C}_{21}\text{H}_{20}\text{O}_2$: C, 82.86; H, 6.62; mol. wt., 304.

Found: C, 82.80; H, 6.51; mol. wt., 308.

α, δ -Diphenyl- α -cyclopentyl- δ -hydroxybutanolide, Saponification of 0.2 g. of α, δ -diphenyl- α -cyclopentyl- $\Delta^{\beta\delta}$ -butenolide with 30 ml. of 2% sodium hydroxide and 8 ml. of ethanol at reflux temperature for 20.5 hours gave a quantitative crude yield of the product as a glass. Successive recrystallizations from hexane-ether, benzene-hexane and aqueous methanol gave 0.17 g. (81%), m.p. $106.5-110^\circ$ of an analytical sample, infrared absorption (KBr), 2.98, 3.36 and 5.73μ .

Anal. Calcd. for $\text{C}_{21}\text{H}_{22}\text{O}_3$: C, 78.23; H, 6.88; mol. wt., 322.

Found: C, 78.36; H, 6.78; neu. eq., 323.

α, α -Dibenzyl- γ -methyl- $\Delta^{\beta\delta}$ -butenolide (XVII). From α -

Angelica lactone. A mixture of sodium hydride (1.5 g., 0.0625 mole), benzyl chloride (6.3 g., 0.0495 mole), and 30 ml. of dry dimethyl sulfide was stirred magnetically under a nitrogen atmosphere. A solution of α -angelica lactone (XV) (2.5 g., 0.025 mole) in 5 ml. of benzene was added dropwise over a one hour period. A vigorous evolution of hydrogen was observed. The flask was cooled in cold water to moderate the exothermic reaction. Stirring was continued for an additional 2.5 hours. The reaction mixture was filtered and the filtrate poured into 800 ml. of water. The slightly basic mixture was extracted with benzene. The organic phase was dried over sodium sulfate and examined by vapor phase chromatography on a 6 foot column of 5% QF-1, column temperature 212° , with helium as carrier gas at 50 p.s.i., and at sensitivity 100X1 using a Micro-Tek GC-1600. The only peak obtained corresponded to that of authentic (XVII). The solvent was removed from the organic phase by an air stream to give 5.19 g. (73%) of the crude butenolide (XVII). Recrystallization from benzene-hexane afforded 3.62 g. of (XVII), m.p. $160-160.5^{\circ}$ and a second crop of 0.3 g. of (XVII), m.p. $158.5-160^{\circ}$ for a total recrystallized yield of 55%.

From the aqueous phase, after the usual work up and recrystallization from benzene-hexane, there was obtained 0.52 g. of oily crystals. A recrystallization from benzene-hexane afforded 0.2 g. (2.6%) of the pseudo acid (XXI) described below, m.p. $108.5-111.5^{\circ}$.

An analytical sample of (XVII) was obtained from a previous reaction by recrystallization from methanol and had m.p. $160-160.5^{\circ}$, infrared absorption (KBr), 5.60μ (carbonyl) and 5.95μ (nonconjugated double bond).

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52; mol. wt., 278.

Found: C, 81.98; H, 6.64; mol. wt., 279.

Recrystallization of the neutral material from a similar benzylation reaction (double quantities of reactants used) from ethanol, gave a 17% yield of (XVII) and 8.67 g. of chromatographed oil. This oil had carbonyl absorption at 5.80μ . A 3.15 g. sample of this oil was rechromatographed on 63 g. of alumina using hexane-benzene (9:1). A trace of (XVII) was found in the first fraction. The second fraction (1.23 g.) was submitted to vapor phase chromatography on a 6 foot U-shaped glass column of 5% SE 30, column temperature 195° , with argon as carrier gas at 60 p.s.i., and at sensitivity 1 using a Barber Colman Model 15. Three components were detected: 1. butenolide (XVII), 2.4%, retention time 2.3 minutes; 2. component "A", 88.7%, retention time 4 minutes; 3. component "B", 8.9%, retention time 18.5 minutes. This mixture crystallized after several months and several recrystallizations from pentane gave a material m.p. $65-66^\circ$. Vapor phase chromatography of this 66° material indicated that it was practically pure component "A" (only a very slight trace of the "B" component was detected. N.m.r. ($CDCl_3$), τ values: 2.82 (center of multiplet, 10H); 5.95 (center of quadruplet, 2H); 6.82 (center of doublet, 4H); 7.53 (singlet, 2H); 8.0 (singlet, 3H); 8.86 (center of triplet, 3H). On the basis of this spectrum the ethyl ester of α,α -dibenzyllevulinic acid is indicated. This ethyl ester had infrared absorption (KBr) 5.76 (shoulder) and 5.89μ .

Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46; O, 14.79; mol. wt., 324.

Found: C, 77.58; H, 7.33; O, 15.19; mol. wt., 346.

Fraction three (1.44 g.) from this column chromatography

(contained only a trace of XVII) was saponified with 25 ml. of 10% sodium hydroxide and 5 ml. of ethanol for 18 hours and gave 1.45 g. of crude acid. Recrystallization of this crude acid from benzene-hexane gave 1.23 g. (94%) of the pseudo acid α,α -dibenzyl- δ -methyl- δ -hydroxybutanolid (XXI), m.p. 109-110°. A mixed melting point with the analytical sample described next was not depressed.

Saponification of 0.5 g. of butenolid (XVII) with 25 ml. of 10% sodium hydroxide and 5 ml. of ethanol for 23.5 hours gave a quantitative yield of the pseudo acid (XXI) m.p. 109-111°, from benzene. An analytical sample after 3 recrystallizations from benzene-hexane had m.p. 111-113°. This pseudo acid (XXI) had infrared absorption (KBr), 2.92 and 5.70 μ .

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80; mol. wt., 296.

Found: C, 77.50; H, 6.69; neu. eq., 294.

A 2,4-dinitrophenylhydrazone of this acid was prepared using ethanolic 2,4-dinitrophenylhydrazine and hydrochloric acid; three recrystallizations from ethanol gave an analytical sample, m.p. 217° (dec.).

Anal. Calcd. for $C_{25}H_{24}O_6N_4$: C, 63.01; H, 5.08; N, 11.76.

Found: C, 62.62; H, 5.09; N, 11.89.

From β -Angelica lactone. A mixture of sodium hydride (3 g., 0.125 mole) and 50 ml. of dry dimethyl sulfoxide was stirred magnetically under a nitrogen atmosphere. A few drops of a solution of β -angelica lactone (5.89 g., 0.06 mole) in 10 ml. of benzene was added to start the reaction (a somewhat slower reaction than with α -angelica lactone) followed by the rest of the solution along with benzyl chloride

(15.2 g., 0.12 mole) in 10 ml. of benzene over a one hour period. The exothermic reaction was kept below 43° by use of a cold water bath. The reddish colored solution was stirred for an additional 2.5 hours. The reaction mixture was filtered, and the filtrate poured into 1.5 l. of water and extracted with benzene. Removal of the solvent from the organic phase in vacuo gave 14.04 g. of a crude oil. Recrystallization of the crude oil from ethanol-benzene (20:1) gave 3.39 g. (20.5%) of the product (XVII) m.p. 158.5-160°. The solvent free residue (10.7 g.) was chromatographed on alumina using benzene. The main fractions, after removing some noncarbonyl material, consisted of 6.89 g. of oil with similar properties as the oil from the α -angelica lactone reaction above. A 6 g. sample of this oil was rechromatographed on 140 g. of alumina using benzene. Each fraction was examined by vapor phase chromatography using the same conditions as previously described. Results are as follows:

Forerun 0.01 g. of benzyl chloride (discarded)

			XVII	Comp. "A"	?	Comp. "B"
Fraction 1.	25 ml.	1.58 g.	14%	76%	6%	3%
"	2. 25 ml.	1.28 g.	1.8%	26%	-	71.5%
"	3. 40 ml.	0.77 g.	0.9%	19.6%	-	79.5%
"	4. 50 ml.	0.43 g.	-	13%	-	87%
EtOAc	5. 100 ml.	1.61 g.	-	4%	-	96%

In addition to the crystalline product (XVII) the VPC indicated the presence of an additional 0.05 g. of (XVII) in the oil, which represents a total yield of (XVII) of 20.6%. The total amount of the ethyl ester (component "A") as indicated by the VPC was 2.13 g. and component "B" amounted to 3.50 g., the ratio of "A" to "B" was 1:1.6.

AN NMR spectrum of fraction 5 above indicated (CDCl_3), τ values of: 2.9 (center of multiplet, 15H); 5.0 (singlet, 2H); 6.79 (center of

quadruplet, 4H); 7.58 (singlet, 2H); 8.10 (singlet, 3H). This spectrum of the "B" component is in agreement for benzyl α, α' -dibenzyllevulinate.

From Michael Dimer (XVI). The reaction of sodium hydride (0.8 g., 0.033 mole) in 30 ml. of dry dimethyl sulfoxide with 3.13 g. (0.016 mole) of the dimer (XVI) and benzyl chloride (4.09 g., 0.032 mole) in 3 ml. of dimethyl sulfoxide for a total of 1.75 hours, using the same procedure as described for β -angelica lactone, gave a moderately vigorous reaction as in the case of β -angelica lactone. The resulting reaction mixture was tan colored. The reaction mixture was filtered and the filtrate poured into 800 ml. of water and the basic mixture extracted with benzene. The organic phase after removing the solvent was recrystallized from benzene-methanol (1:30), giving 1.32 g. of butenolide (XVII), m.p. 160-160.5^o; and a second crop of 0.06 g. of less pure (XVII), m.p. 132-155^o. The solvent free residue (2.43 g.) from the recrystallization was chromatographed on 50 g. of alumina using benzene. Each fraction was examined by vapor phase chromatography using the Barber Colman Model 15 with the same conditions as described above. Results are as follows:

Forerun only benzyl chloride (discarded)

				XVII	Comp. "B"
Fraction	1.	10 ml.	0.02 g.	100%	-
"	2.	25 ml.	0.34 g.	38.5%	61.5%
"	3-4.	50 ml.	0.25 g.	-	100%
EtOAc	5.	70 ml.	1.14 g.	-	Mostly "B" plus some ? oil.

The yield of butenolide (XVII) was 1.39 g. (15.5%) of crystalline material, in addition to 0.15 g. of (XVII) in the oil which represents a total yield of (XVII) of 17.1%. The total yield of component "B" amounted to 0.45 g.

A sample of fraction 3 above was saponified to give (in good yield) the same pseudo acid (XXI) as that obtained from the parent butenolide (XVII).

α,α,γ -Trimethyl- $\Delta^{\beta,\gamma}$ -butenolide (XIX). From α -Angelica lactone. A mixture of sodium hydride (3 g., 0.125 mole), methyl iodide (20 g., 0.141 mole), 20 ml. of dry dimethyl sulfoxide and 20 ml. of benzene was stirred magnetically under a nitrogen atmosphere. A solution of α -angelica lactone (XV) (4.9 g., 0.05 mole) in 10 ml. of benzene was added at a rate to keep the temperature of the flask contents below 38° (cooling as necessary). The reaction mixture thickened after adding about one half of the butenolide solution; an additional 30 ml. of benzene and 10 g. of methyl iodide was added and stirring was continued for a total of 2 hours. The large amount of sludge was filtered off (this residue gave a strong iodide ion test) and the filtrate was poured into 500 ml. of water and the neutral mixture was extracted with benzene. Work up of the organic phase, after removing the solvent, gave 5.1 g. (81%) of the crude product (XIX). This trimethyl butenolide (XIX) was somewhat volatile at room temperature. Fractionation of the remaining product (4.8 g.) afforded 3.07 g. of pure (XIX) (b.p. 82-83° at 41 mm., n_D^{25} 1.4318) and 1.11 g. of less pure product, b.p. 83-88° at 42 mm. The total recovery of (XIX) was 4.18 g. (66%); with infrared absorption (neat, of 83° material) 3.34 μ with shoulders at 3.37 and 3.46 μ (CH₃), 5.55 μ (carbonyl) and 5.94 μ (nonconjugated double bond). The recorded value is b.p. 59° at 18 mm. (33).

From β -Angelica lactone. A mixture of sodium hydride (3 g., 0.125 mole) and 50 ml. of dry dimethyl sulfoxide was stirred magnetically

under a nitrogen atmosphere. A few drops of β -angelica lactone (XVIII) (4.9 g., 0.05 mole) was added to initiate the reaction; the rest of the butenolide and 20 g. (0.141 mole) of methyl iodide was added over a one hour period, keeping the temperature below 38° . An additional 10 g. of methyl iodide was added and stirring was continued for another hour. Addition of 20 ml. of ether to the clear solution (only small amount of sodium hydride visible) caused a white precipitate to form. The precipitate was filtered off (approx. 10 g. of NaI, strong iodide ion test) and the filtrate was poured into 800 ml. of water. The neutral mixture was extracted with ether; usual work up gave 2.66 g. (42%) of the crude product (XIX). The material balance for this reaction was not good, indicating either evaporation of some of the product during the interim or else incomplete extraction with ether. Flash distillation of this small amount of crude product gave 0.52 g. of (XIX), b.p. $73-83^{\circ}$ at 41 mm., n_D^{25} 1.4308. Saponification of this material gave, the known, -dimethylevulinic acid m.p. $75-79^{\circ}$; see also below.

α,α -Dimethylevulinic acid. α,α,γ -Trimethyl- $\Delta^{\beta\gamma}$ -

butenolide (XIX) from methylation of α -angelica lactone (1.27 g.) was saponified using 12 ml. of 10% sodium hydroxide for 4 hours at reflux temperature (the odor of the butenolide was noticed escaping at the top of the condenser). The usual work up and recrystallization from benzene-hexane gave only 0.31 g. of the acid (21.5%) m.p. $76-78^{\circ}$. The rest of the butenolide had apparently escaped from the flask prior to its reaction. A recrystallization from benzene-hexane gave 0.23 g. (16%) of the acid as thin plates m.p. $77.5-78.5^{\circ}$. A neutralization equivalent gave a value of 143, the molecular weight is 144. The recorded value

is m.p. 75.5-76.5° (37).

A 2,4-dinitrophenylhydraxone of this acid after 3 recrystallizations from ethanol had m.p. 215° (dec.).

Anal. Calcd. for $C_{13}H_{16}O_6N_4$: C, 48.15; H, 4.97; N, 17.28.

Found: C, 48.01; H, 4.81; N, 17.28.

α,α -Dibenzyl- γ -phenylbutyric acid (III). A solution of 2 g. (0.006 mole) of α,α -dibenzyl- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (II) in 125 ml. of ethyl acetate with 0.4 g. of 10% Pd.c, was hydrogenated at 30° and 43 p.s.i. of hydrogen in a Parr apparatus for 12.5 hours. The mixture was filtered (Celite) and concentrated to 5 ml. To the hot solution was added 5 ml. of hexane and the solution set aside to cool. There was obtained 1.18 g. of the acid (III), m.p. 126-127°. Further concentration afforded an additional 0.77 g. of the acid, m.p. 123.5-126° in an overall crude yield of 96.5%. Two recrystallizations from benzene-hexane (only small losses) gave an analytical sample m.p. 126-127°, infrared absorption ($CHCl_3$) 5.90 μ .

Anal. Calcd. for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02; mol. wt., 344.

Found: C, 83.57; H, 7.25; neu. eq., 341.

2,2-Dibenzyl-1-tetralone (IV). From α,α -Dibenzyl- γ -phenylbutyric acid. The general Friedel-Crafts acylation procedure of Johnson and Glenn (38) was followed. In a 100 ml. round bottom flask containing a stoppered port for a capillary bleed and protected by a calcium chloride drying tube, was placed 2 g. (0.006 mole) of α,α -dibenzyl- γ -phenylbutyric acid (III), 1.33 g. (0.006 mole) of phosphorous pentachloride, and 4 ml. of dry benzene. The evolution of hydrogen chloride started immediately, and was over in 15 minutes. The capillary

bleed was inserted and the drying tube replaced with a side arm adapter, equipped with an addition funnel and take off condenser. The volatile phosphorous compounds were removed by distilling with three 15 ml. portions of dry benzene under reduced pressure, while admitting dry air through the capillary. The crude acid chloride and two 7 ml. benzene rinses of the flask were added, over a 15 minute period, to 1.07 g. (0.008 mole) of anhydrous aluminum chloride and 60 ml. of dry benzene which was kept at 10°. After rinsing the funnel with 15 ml. of dry benzene the solution was stirred for 3 hours while the temperature was allowed to rise up to but not above 24°. The mixture was poured into a beaker, cooled in ice water and 50 ml. of ether was added followed by 100 ml. of cold 6N hydrochloric acid with stirring so that the temperature was kept below 15°. The organic phase was separated, washed with three 30 ml. portions of 6N hydrochloric acid, followed by water, 10% sodium hydroxide, and finally with water until free of base. The organic phase was dried with sodium sulfate, filtered, and concentrated to dryness. The oil was recrystallized from ethanol. There was obtained 1.45 g. of the tetralone (IV), m.p. 100-101°, and by concentrating, an additional 0.09 g. (m.p. 97-99°) was obtained (81% crude yield overall). The first crop was recrystallized from ethanol twice to give 1.22 g. of an analytical sample m.p. 100-101°, infrared absorption (CHCl_3) 5.95 μ .

Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{O}$: C, 88.31; H, 6.79.

Found: C, 88.59; H, 6.68.

From 1-Tetralone. A mixture of 4.22 g. (0.176 mole) of sodium hydride (from sodium hydride in oil after extracting the oil with

benzene) and 100 ml. of dry benzene was stirred while a solution of 12.24 g. (0.084 mole) of 1-tetralone, and 23 g. (0.182 mole of benzyl chloride, in 20 ml. of benzene was added dropwise at reflux over a 3 hour period. It was necessary to add several drops of ethanol to initiate hydrogen evolution from the reaction mixture. The mixture was refluxed for an additional 15.5 hours. The light yellow reaction mixture was filtered, washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was flash distilled through a Vigreux column. The first fraction of 3.94 g. (b.p. 131-195° at 0.5 mm.) which probably contains mostly monobenzyl tetralone was recrystallized from ethanol. There was obtained 0.95 g. (m.p. 96-99°) of tetralone (IV). The second fraction of almost pure (IV) 19.49 g. (b.p. 195-210° at 0.5 mm.) was recrystallized from ethanol. There was obtained 18.1 g. of (IV), m.p. 99.5-100.5°. The total crude yield of (IV) was 20.44 g. or 75%. The yield of recrystallized (IV) was 70%. Recrystallization from ethanol raised the melting point to 100-101°. A mixed melting point with the material prepared above was not depressed. Several different attempts to prepare the dinitrophenylhydrazones, semicarbazones, and oxime derivatives all resulted in failure.

α,α -Dibenzyl- γ -phenylbutanolide (VII). A solution of 4 g. (0.012 mole) of α,α -dibenzyl- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (II) in 160 ml. of ethyl acetate with 0.8 g. of Pt/C was hydrogenated at 32° and 46 p.s.i. of hydrogen in a Parr apparatus for 6 hours. The mixture was filtered (Celite) and the filtrate evaporated to dryness. The residue was taken up in carbon tetrachloride and extracted with dilute sodium carbonate solution. The organic phase was washed free of base, dried over

sodium sulfate, and evaporated to dryness. There was obtained 2.49 g. of almost pure (VII) as a light yellow oil in 62% yield. Recrystallization of the oil from benzene-hexane (1:1), gave 1.01 g. of (VII) m.p. 114-115.5°. An additional recrystallization raised the melting point to 116-116.5°. An analytical sample from a previous preparation had m.p. 115.5-116.5°, infrared absorption (CHCl_3) 5.68 μ .

Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{O}_2$: C, 84.17; H, 6.47.

Found: C, 84.12; H, 6.62.

The aqueous phase was acidified with hydrochloric acid, extracted with carbon tetrachloride, dried over sodium sulfate, and evaporated to dryness. There was obtained 1.21 g. of almost pure acid (III) as a colorless oil in 30% yield. Recrystallization of the acid from benzene-hexane gave 0.64 g. of (III) m.p. 120-122°. An additional recrystallization raised the melting point to 121-122°. A mixed melting point with the previously described α,α -dibenzyl- γ -phenylbutyric acid (III) was not depressed.

α,α -Dibenzyl- γ -valerolactone (XXII). From α,α -Dibenzyl- γ -methyl- $\Delta^{\beta\gamma}$ -butenolide. Hydrogenation of the dibenzyl butenolide (XVII) (0.56 g., 0.002 mole) in 15 ml. of ethyl acetate with 0.3 g. of 5% Pt.C required 7.5 hours at atmospheric pressure for hydrogen absorption to cease; 48 ml. (0.0021 mole) of hydrogen (corrected to standard conditions) was absorbed. The catalyst was filtered (Celite) and the solution was extracted with dilute sodium carbonate solution. From the aqueous phase was obtained, after the usual work up, 0.08 g. (14%) of crude α,α -dibenzylvaleric acid (XXIII), infrared absorption (neat), 5.90 μ . An attempt to prepare the amide of this crude acid using

thionyl chloride and conc. ammonium hydroxide failed.

The organic phase was dried over sodium sulfate and evaporated to dryness. The residue was recrystallized from benzene-hexane to give 0.47 g. (83.5%) of the lactone (XXII) m.p. 96-106°. A recrystallization from benzene-hexane raised the melting point to 108-108.5° (59%).

From γ -Valerolactone. A mixture of sodium hydride (5 g., 0.21 mole), benzyl chloride (25.3 g., 0.2 mole), 40 ml. of dimethyl sulfoxide and 30 ml. of benzene was stirred magnetically under a nitrogen atmosphere. A solution of γ -valerolactone (redistilled, b.p. 103° at 29 mm., n_D^{25} 1.4312, 10 g., 0.1 mole) in 10 ml. of benzene was added dropwise over a one hour period at room temperature. The exothermic reaction caused the solution to reflux gently. Stirring was continued for an additional 5 hours. The mixture was filtered to remove a large amount of sodium chloride, and the filtrate was poured into 800 ml. of water and was extracted with benzene and dilute sodium carbonate. The aqueous phase was discarded.

The organic phase was dried over sodium sulfate and the solvent removed in vacuo. There was obtained 25.25 g. of oily crystals in 91% crude yield. The crude lactone (XXII) was recrystallized from benzene-hexane to give 9.2 g. of (XXII) m.p. 107-109°, and a second crop of 7.25 g., m.p. 92-108° was obtained by concentrating the mother liquor. The residue from the recrystallization, after removing the solvent, (8.33 g.) was chromatographed on 160 g. of alumina using hexane-ether (1:1) as eluant.

Fractions 1-3 gave 2.82 g. of material having no carbonyl absorption. Fraction 2 had m.p. 0-5°, n_D^{25} 1.5582 and gave a molecular

weight value of 194. It decolorized permanganate and gave a dibromide m.p. 233° dec. from ethanol (meso stilbene dibromide has m.p. 237°). Treatment of this material with conc. hydrochloric acid or benzenesulfonic acid did not produce any carbonyl absorption. It had characteristic infrared absorption (neat) in microns as follows (* denotes shoulder, s-strong, m-medium): 3.28s, 3.49s, 6.23m, 6.30*, 6.68s, 6.88s, 7.10*, 7.20m, 7.35s, 8.30s, 9.1-9.4s, 9.73s, 11.06m, 13.4-13.75s and 14.35-14.45s. This material was not examined further but is probably cis stilbene (39). Based on benzyl chloride this 2.82 g. represents a 16% yield of cis stilbene. Fraction 4 gave 1.16 g. of uncharacterized material (carbonyl absorption 5.58μ shoulder, 5.66 and 5.78μ) but is probably a mixture of γ -valerolactone and the mono and dibenzyl derivatives. Fraction 5 and 6 gave 2.42 g. which when recrystallized from benzene-hexane gave 1.21 g. of the product (XXII) m.p. $105.5-109.5^{\circ}$.

The total yield of (XXII) was 17.66 g. (63%). An analytical sample was obtained after 2 recrystallizations from benzene-hexane and had m.p. $109-109.5^{\circ}$. A mixed melting point with the product obtained from the hydrogenation above was not depressed, and the infrared spectra were identical (KBr), 5.70μ .

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19.

Found: C, 81.33; H, 7.16.

Attempted Isomerization of γ -Methyl- $\Delta^{\beta\gamma}$ -butenolide to the $\Delta^{\alpha,\beta}$ -Isomer. Formation of Michael Dimer (XVI). The isomerization procedure described by Ramirez and Rubin (7) was used. Freshly distilled γ -methyl- $\Delta^{\beta\gamma}$ -butenolide (XV) (8.8 g., 0.09 mole) and 2 ml.

of triethylamine was heated to reflux for 4 hours. Fractionation gave 2.47 g. (28%) of recovered butenolide (XV) and 4.67 g. of material which was not the expected β -angelica lactone (XVIII). This material had b.p. 200-205° at 8 mm., n_D^{25} 1.4946. A molecular weight value of 201 (expected mol. wt. 196) was obtained for this oil. After standing six months some oily crystals were obtained which when washed with benzene-hexane had m.p. 73-83°. A satisfactory solvent for recrystallization could not be found. This material does not give a dinitrophenylhydrazone with Shine's reagent (9). The yield of this dimer (XVI) based on recovered (XV) was 75% (53% conversion). The literature values for this dimer (28) are m.p. 85-85.5°, b.p. 110-175° at 2.5 mm. N.m.r. (CHCl_3), τ values: 2.50 (center of doublet, 1H); 3.88 (center of doublet, 1H); 5.62 (center of multiplet, 1H); 7.32 (center of triplet, 3H); 8.49 (singlet, 3H); 8.63 (center of triplet, 3H).

Michael Dimer of α -Benzyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (XLI).

This procedure is essentially that of Mark (26). To a stirred suspension of lithium aluminum hydride (3.5 g., 0.092 mole) in 500 ml. of dry ether was added α -benzylidene- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide (26) (9.8 g., 0.04 mole) in two equal portions, the second 5 minutes after the first. Stirring was continued for 2.5 hours after which the yellow color of the starting butenolide was still present. An additional 0.5 g. of lithium aluminum hydride was added and stirring was continued for another hour (the color still remained). The excess hydride was decomposed by adding 200 ml. of wet ether, followed by 50 ml. of water dropwise over a 25 minute period, with cooling in ice water. The mixture was stirred for 45 minutes and then filtered. The ether phase was washed free of base,

dried over sodium sulfate, and concentrated. There was obtained 2.83 g. of the dimer (XLI), m.p. 154-158°, in 29% yield. Recrystallization from ethanol raised the melting point to 160-161° (negligible loss), infrared absorption (CHCl₃) 5.65 μ , but in (KBr) 5.59 and 5.67 μ ; calculated for (C₃₄H₂₈O₄), a molecular weight of 501; found molecular weight of 495 and 498.

Mark (26) gives m.p. 161-162° and carbonyl absorption at 5.69 μ , and formulated this material as α -benzyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (unproved). N.m.r. (CDCl₃), τ values: 2.85 (center of multiplet, 20H); 3.70 (center of multiplet, 1H); 4.79 (center of doublet, 1H); 6.49 (singlet, 2H); 7.15 (center of multiplet, 4H).

Oxidative Dimer of α,γ -Diphenyl- $\Delta^{\alpha,\beta}$ -butenolide (XXXI).

The procedure of Baddar and Sherif was used (10). α -Phenyl- β -benzoyl-propionic acid (10 g., 0.039 mole), 20 ml. of acetic acid and 40 ml. of concentrated sulfuric acid was heated on a steam bath for 1.5 hours. The rust colored paste was cooled and poured into ice water. The orange colored precipitate was filtered and washed successively with water, 10% sodium carbonate (the precipitate turned yellow and the filtrate was purple), and finally with water until the filtrate was no longer basic and had no purple color. The precipitate was dried in vacuo. There was obtained 7.71 g. of lemon yellow powder m.p. 282° dec. in 83% yield. A sample was recrystallized from boiling nitrobenzene (thermochromic behavior noted) and had m.p. 288-290° dec. (evacuated capillary), infrared absorption (KBr), 5.70 μ . The reported constants are m.p. 288-289° dec., infrared absorption (KBr), 5.68 μ (11).

Formation of Michael Dimer (XXXII) from Oxidative Dimer (XXXI).

One gram of dimer (XXXI) was saponified with 1 g. of sodium hydroxide in

30 ml. of diglyme and 15 ml. of water at reflux temperature for 17 hours. This dark red solution was found difficult to work up, since dilution with water caused a dark gummy tar to deposit. The tar could be separated by acidification and extraction with benzene. Three phases formed. The tar in the bottom phase was discarded, the middle yellow cloudy phase was repeatedly extracted with benzene to give, 1.02 g. of crude oily crystals; the upper benzene phase contained oily tars and was discarded. Recrystallization of the crude crystals above from benzene-hexane gave 0.55 g. of neutral brown crystals m.p. 246-247°. Recrystallization from benzene (Norite) gave 0.38 g., of colorless (XXXII), m.p. 246-247° (clear melt). Further recrystallization did not change the melting point; infrared absorption (KBr), 5.62 μ . A mixed melting point with the starting dimer was depressed. N.m.r. (CDCl₃), τ values: 2.8 (center of multiplet, 20H); 5.90 (center of weak doublet, 2H); 6.80 (singlet, 1H); 7.08 (singlet, 1H).

Anal. Calcd. for C₃₂H₂₄O₄: C, 81.34; H, 5.12; mol. wt., 473.

Found: C, 81.63; H, 4.95; mol. wt., 476.

C, 80.97; H, 5.30.

Under different conditions, one gram of dimer (XXXI) was refluxed with 10 ml. of 10% sodium hydroxide and 20 ml. of ethylene glycol for 41 hours. Diluting the reaction mixture and extracting with benzene gave 0.01 g. of acetophenone (approx. 2%) determined as the 2,4-dinitrophenylhydrazone using Shine's reagent (9), m.p. 246-247° dec. (infrared spectrum was identical with that of authentic acetophenone dinitrophenylhydrazone). Work up of the aqueous phase gave a mixture of acidic and neutral material. This mixture was reextracted with dilute sodium

hydroxide and benzene to give, after work up of the organic phase, 0.14 g. (14%) of the dimer (XXXII), m.p. 244-246° (infrared spectrum identical with the above material). The aqueous phase after work up, gave 0.5 g. (47%) of α -phenyl- β -benzoylpropionic acid m.p. 155-156°. The overall recovery of material was reduced by some tar formation, but not as much as in the diglyme reaction above.

Formation of Michael Dimer (XXXIII). The procedure of Yates and Clark was used (11). α -Phenyl- β -benzoylpropionic acid (7.63 g., 0.03 mole) and 15 ml. of acetic anhydride was heated at 100° under a nitrogen atmosphere for 16 hours. The solvent was removed in vacuo to give a light yellow glass. Recrystallization of the glass from benzene in the presence of air gave 3.31 g. of dimer (XXXIII), m.p. 225-233° (47%). A second crop afforded 1.69 g. of the oxidative dimer (XXXI), m.p. 283° dec. (24%) (recrystallized m.p. 289-290° dec.).

Two recrystallizations of the first crop material, from benzene, gave an analytical sample m.p. 233.5-234.5°, infrared absorption (KBr), 5.70 μ . A mixed melting point with the Michael dimer (XXXII) and the oxidative dimer (XXXI) gave depression for both. N.m.r. (CDCl₃), τ values: 2.78 (center of multiplet, 2H); 4.47 (broad singlet, 1H); 6.27 (center of multiplet, 2H).

Anal. Calcd. for C₃₂H₂₄O₄: C, 81.34; H, 5.12; mol. wt., 473.

Found: C, 81.32; H, 4.82; mol. wt., 482, 498.

One gram of this dimer (XXXIII) was refluxed with 20 ml. of 5% sodium hydroxide and 5 ml. of diglyme for 30 hours. α -Phenyl- β -benzoylpropionic acid (0.92 g., 86%), m.p. 154.5-155° was obtained by work up of the aqueous phase. Acetophenone (approx. 0.01 g.) was

obtained from the organic phase (determined as the dinitrophenylhydrazone derivative m.p. 243-246° dec.).

Oxidative Dimer of α -Methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (XXXIV).

The procedure of Ramirez and Rubin was used (7). α -Methyl- β -benzoyl-propionic acid (1 g., 0.0052 mole) and 4 ml. of acetic anhydride was heated on a steam bath for 3 hours. The crude mixture was taken up into ether and extracted with 10% sodium carbonate solution. The organic phase afforded 0.3 g. (33%) of the dimer (XXXIV), m.p. 227-230°, infrared absorption (CHCl_3), 5.70 μ .

Several recrystallizations of this material from benzene gave an analytical sample m.p. 232.5-233° dec., infrared absorption (KBr), 5.67 μ . N.m.r. (CDCl_3), τ values: 2.65 (center of multiplet, 12H); 8.41 (center of doublet, 6H).

Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{O}_4$: C, 76.28; H, 5.24; mol. wt., 346.

Found: C, 76.61; H, 5.20; mol. wt., 342, 350.

Refluxing this dimer (0.19 g.) with 30 ml. of 10% potassium hydroxide for 2.5 hours afforded 0.18 g. (86%) of α -methyl- β -benzoyl-propionic acid m.p. 142.5-143°.

Michael Dimer of α -Methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (XXXV).

From Butylation of α -Methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide. A reaction identical to the butylation reaction of (IX) already described (except that double amounts of reactants were used) gave 0.27 g. of a new product (from chromatography of the residues from the recrystallization) in 8.5% crude yield. Two recrystallizations from benzene-hexane gave 0.04 g. (1.15%) of (XXXV), m.p. 178-179°, identical (infrared spectrum) to the material described next.

From Attempted Benzoylation of α -Methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide. α -Methyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide (IX) (4 g., 0.023 mole), sodium hydride (0.6 g., 0.025 mole) and methyl benzoate (3.13 g., 0.023 mole) in 50 ml. of dimethyl sulfoxide and 15 ml. of benzene (using the same procedure as previously described for the butylation reaction) for 2 hours at room temperature under a nitrogen atmosphere did not give any of the benzoyl derivative (XLII). Chromatography of the crude neutral material (5.55 g.) on 112 g. of alumina using benzene as eluant, gave 5.8% of the oxidative dimer (XXXIV) (m.p. 232-233° dec. after recrystallization) and 0.84 g. (21%) of the practically pure Michael dimer (XXXV), m.p. 179-179.5° after recrystallization. From the alumina there was obtained 0.07 g. (1.6%) of α -methyl- β -benzoylpropionic acid, m.p. 136.5-141°.

An analytical sample of the dimer (XXXV) was obtained from methanol m.p. 179-179.5°, infrared absorption (KBr), 5.65 μ . N.m.r. (CDCl₃), τ values: 2.8 (center of multiplet, 1H); 4.77 (center of doublet, 1H); 7.45 (center of multiplet, 2H); 8.07 (singlet, 3H); 8.70 (center of doublet, 3H).

Anal. Calcd. for C₂₂H₂₀O₄: C, 75.84; H, 5.79; mol. wt., 348.

Found: C, 75.88; H, 5.44; mol. wt., 350.

A sample of this dimer (XXXV) (0.18 g.) was refluxed with 20 ml. of 10% sodium hydroxide and 3 ml. of ethanol for 13 hours. No unsaponified material was recovered. The aqueous phase, after work up and recrystallization from benzene-methanol, afforded 0.15 g. of crude lactone acid (XXXVI) as 3 crops (79%). Recrystallization of a sample twice from aqueous methanol gave an analytical sample of (XXXVI) m.p. 246-247°

dec., infrared absorption (KBr), 5.61 and 5.86 μ . N.m.r. (CDCl₃), τ values: 2.7 (center of multiplet, 10H); 4.36 (broad singlet, 1H); 6.33 (broad singlet, 1H); 8.74 (rough singlet, 3H); 9.11 (center of doublet, 3H). The remaining hydrogens could not be accurately established.

Anal. Calcd. for C₂₂H₂₂O₅: C, 72.11; H, 6.05.

Found: C, 71.92; H, 5.91.

Benzoylation of γ -Methyl--butenolide. A mixture of sodium hydride (2.64 g., 0.11 mole) and 300 ml. of dry dimethylformamide was stirred magnetically at room temperature under a nitrogen atmosphere. A solution of α -methyl--butenolide (XV) (4.9 g., 0.05 mole) and benzoyl chloride (14.4 g., 0.1 mole, dried over CaH₂) was added dropwise over a one hour period. A 4° temperature rise was noted. Stirring was continued for an additional 3 hours, after which the evolution of gas appeared to be over. The reaction mixture was filtered and the filtrate poured into 2.5 l. of water and the acid solution was extracted with benzene. The organic phase was dried with sodium sulfate and the solvent removed in vacuo. The residue (9.3 g.) was recrystallized from benzene-methanol to give one gram (6.5%) of crude yellow furan (XLII), m.p. 117-135°. The mother liquor after removing the solvent was chromatographed on alumina but only uncharacterized oils and acids were obtained. One fraction from a similar reaction gave a positive nitrogen test upon sodium fusion.

Recrystallization of the crude furan (XLII) from benzene-methanol gave 0.55 g. (3.6%), m.p. 137-142°. Successive recrystallizations from benzene-methanol, benzene-hexane, and aqueous methanol afforded an analytical sample, m.p. 141-142° of yellow needles, infrared

absorption (CHCl_3), 5.65, 5.72 and 6.10 μ . This product gave a negative nitrogen and halogen sodium fusion and does not form a dinitrophenylhydrazones.

N.m.r. (CDCl_3), τ values: 1.82 (center of multiplet, 2H); 2.54 (center of multiplet, 8H); 3.91 (singlet, 1H); 7.88 (singlet, 3H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{14}\text{O}_4$: C, 74.45; H, 4.60; mol. wt., 306.

Found: C, 74.22; H, 4.79; mol. wt., 308.

Saponification of a 0.1 g. sample of the furan (XLII) gave only an uncharacterized neutral dark oily material (0.05 g.) (infrared absorption indicated two carbonyl groups at 5.74 and 5.90 μ in addition to aromatic absorption), which did not form a dinitrophenylhydrazones. From the aqueous phase 0.04 g. (quantitative) of benzoic acid m.p. 105-113° (infrared spectrum identical to authentic benzoic acid) was obtained.

α -Benzyl- β -benzoylpropionic acid. From α -Benzylidene- β -benzoylpropionic acid. The benzylidene acid, m.p. 173-174°, obtained by the procedure of Mark (26) (5.33 g., 0.02 mole) was hydrogenated, at 42 p.s.i., in acetic acid in a Parr apparatus with 1 g. of 5% Pt/C for 3 hours. The catalyst was filtered (Celite) and the solvent stripped off in vacuo. The residue was recrystallized from benzene-hexane (Norite) to give 1.46 g. (27%) of the benzyl keto acid, m.p. 160-174°. A recrystallization from benzene gave 1.27 g. (23.5%), m.p. 173.5-175.5°, infrared absorption (KBr), 5.85 and 5.95 μ . A mixed melting point with the starting acid was depressed, m.m.p. 163-168°. The recorded value is m.p. 169.5° (8).

Chromatography of the residue from the recrystallization above on 66 g. of alumina gave 1.35 g. (27%) of an oil, infrared absorption

(neat), 5.66μ (molecular weight 255). This material was not examined further but is probably α -benzyl- γ -phenylbutanolide.

From α -Benzylidene- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide. A modified procedure of Thiele and Mayr was used (8). α -Benzylidene- γ -phenyl- $\Delta^{\beta\gamma}$ -butenolide (9.93 g., 0.04 mole) and 150 ml. of acetic acid was heated on a steam bath and stirred magnetically while 25 g. of a copper-zinc couple (25) was added in 5 g. portions at approximately 5 hour intervals, the reaction was stirred for 3 more hours after the last addition. The total reaction time was 25 hours. The mixture was filtered and the metal residue washed with hot water and hot benzene. The filtrate was poured into 2.5 l. of water and extracted with benzene. The organic fraction was dried and concentrated (Norite). There were obtained two crops of acid (3.23 g.), 2.61 g., m.p. $173.5-175^{\circ}$ and 0.62 g., m.p. $165-172^{\circ}$.

Chromatography of the residue from the recrystallization (6 g.) on 200 g. of alumina with benzene, gave 0.28 g. of a crude dimer (recrystallization from benzene-hexane gave 0.06 g., m.p. $203-212^{\circ}$, 0.6% yield), which had infrared absorption (CHCl_3), 5.66μ . This dimer was not examined further but is probably a γ -bis oxidative dimer of α -benzyl- γ -phenyl- $\Delta^{\alpha,\beta}$ -butenolide. Extraction of the alumina with dilute sodium carbonate gave an additional 0.56 g. of the acid product m.p. $160-169.5^{\circ}$. The total yield of the acid was 3.79 g., 35%. A sample of this acid after recrystallization from benzene had m.p. $173.5-175^{\circ}$.

From Michael Dimer (XLI). This dimer (0.5 g.) was refluxed with 25 ml. of 10% sodium hydroxide and 2 ml. of ethanol for 48 hours. The solution was filtered to remove some silica and a small trace of

unsaponified dimer. The filtrate was acidified, the precipitate was filtered and washed with water. After drying there was obtained 0.53 g. (98%) of the product acid m.p. 172-174°. A recrystallization from benzene gave 0.48 g. (89%) and raised the melting point to 174.5-175.5°.

Hydrogenation of the Michael Dimer (XLI). This dimer (0.5 g., 0.001 mole) was hydrogenated in a Parr apparatus in ethyl acetate at 46 p.s.i. for 17.5 hours with 0.2 g. of 15% Pd.C. The catalyst was filtered (Celite), and the solution was extracted with 10% sodium carbonate. No acidic material was obtained from the aqueous phase. The organic phase was dried and the solvent removed. The residue was recrystallized from benzene-hexane, there was obtained 0.45 g. (90%) of the saturated form of the dimer m.p. 189-193°. A sample was recrystallized from benzene-hexane and benzene-methanol to give an analytical sample, m.p. 192.5-193.5°, infrared absorption (KBr), 5.69 μ .

Anal. Calcd. for $C_{34}H_{30}O_4$: C, 81.25; H, 6.02; mol. wt., 503.

Found: C, 81.48; H, 6.20; mol. wt., 508.

γ -Phenylbutyric acid (VI). γ -Phenyl- $\Delta^{\beta,\gamma}$ -butenolide (I)

(4 g., 0.025 mole) in ethyl acetate was hydrogenated in a Parr apparatus at 45 p.s.i. with 0.8 g. of 10% Pd.C for 16 hours. The catalyst was filtered (Celite), and the solvent was removed by an air stream. A light yellow oil (3.68 g.) was obtained in 90% yield. The infrared spectrum of this oil was identical to that of the purified acid (VI). In contrast to the Pt/C reaction below no neutral material was indicated by infrared examination. The oil was flash distilled to give 2.32 g. (56.5%) of the product (VI), b.p. 126-129° at 0.5 mm., m.p. 47.5-49.5°. A mixed melting point with authentic γ -phenylbutyric acid (m.p. 50.5-51°) was m.m.p. 48-50°.

γ -Phenylbutanolide (VIII). γ -Phenyl- $\Delta^{\beta,\gamma}$ -butenolide (I)

(2.3 g., 0.0144 mole) in ethyl acetate was hydrogenated in a Parr apparatus at 45 p.s.i. with 0.4 g. of 5% Pt.C for 3 hours. The catalyst was filtered (Celite), and the solvent was removed by an air stream, the oil taken up in benzene and extracted with dilute sodium carbonate. The aqueous phase afforded 1.85 g. (79.5%) of γ -phenylbutyric acid (VI), m.p. 46.5-50°.

The organic phase gave 0.14 g. (6%) of (VII) as an oil which would not crystallize, infrared absorption (neat), 5.60 μ . Recorded value is m.p. 38°, infrared absorption (CCl₄), 5.57 μ (40).

A similar reaction using Adams catalyst afforded the acid (VI) in 93% yield and the butanolide (VIII) in 5% yield.

Ethyl γ -phenylbutyrate. This ester was prepared by the reaction of γ -phenylbutyric acid (VI) with ethanol according to the directions of Hershberg and Fieser (41). The yield was 93% of ester b.p. 146-150° at 18 mm. The recorded value is b.p. 144-147 at 19 mm. (41).

Ethyl α -benzyl- γ -phenylbutyrate. An attempt to dibenzylate ethyl γ -phenylbutyrate using sodium hydride and benzyl chloride in refluxing benzene for 14 hours gave only the monobenzyl product in 48% yield, based on recovered ethyl γ -phenylbutyrate (37% conversion). The redistilled analytical sample had b.p. 172° at 2 mm., $n_D^{25.8}$ 1.5312. An attempt to benzylate this ester in a separate reaction also failed.

Anal. Calcd. for C₁₉H₂₂O₂: C, 80.81; H, 7.85.

Found: C, 80.90; H, 7.87.

Saponification of this ester with alcoholic sodium hydroxide for 19 hours afforded a 98% yield of pure α -benzyl- γ -phenylbutyric

acid. A sample was recrystallized from benzene-hexane and had m.p. 55.5-56.5°. A neutralization equivalent was calculated for 254, found 251.

Ethyl dibenzylacetate. This ester was prepared using the procedure of Cristol, Ragsdale and Meek (42) by benzylation of ethyl acetate using benzyl chloride and sodium hydride. The yield was 60% of flash distilled ester, b.p. 126-142° at 0.5 mm. The recorded value is b.p. 201-203 at 18 mm. (42).

Saponification of a sample of this ester gave a quantitative yield of dibenzylacetic acid m.p. 89-89.5°. The recorded value is m.p. 87-88° (42).

PART II

SUMMARY

1. Seven new α,α -dialkyl butenolides have been prepared by alkylation of butenolides, in addition to two others which are known.
2. Proof of structure for 3 of these, α,α -dibenzyl- δ -phenyl- $\Delta^{\beta,\delta}$ -butenolide, α,α -dibenzyl- δ -methyl- $\Delta^{\beta,\delta}$ -butenolide and α -methyl- α -benzyl- δ -phenyl- $\Delta^{\beta,\delta}$ -butenolide, were obtained using a different method for each.
3. Evidence for the structure of α -methyl- α -butyl- δ -phenyl- $\Delta^{\beta,\delta}$ -butenolide was obtained by isolating a keto acid, from the saponification of this butenolide, which formed a dinitrophenylhydrazone derivative.
4. Evidence for the structure of α,δ -diphenyl- α -cyclopentyl- $\Delta^{\beta,\delta}$ -butenolide was obtained by isolating the pseudo acid form of the keto acid, from the saponification of this butenolide.
5. No δ -alkyl products were isolated from these alkylation reactions.
6. Formation of several different Michael dimers, indicates that the δ -position can be a reaction site under the appropriate conditions.
7. Formation of several previously unreported Michael dimers, under a variety of relatively mild conditions, have been observed.
8. Diacylation of α -angelica lactone indicated that one acyl group was α -attached and the other O-attached.

9. Hydrogenations of butenolides using Pd/C have been observed to give hydrogenolysis of the γ -benzyl position in addition to hydrogenation of the double bond.
10. Hydrogenations of butenolides using Pt/C have confirmed the previously observed formation of a mixture of butanolide and the corresponding butyric acid.
11. These alkylation reactions open a new route to the somewhat difficult to obtain α,α -disubstituted δ -keto acids.

PART II

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