CHEMISTRY OF BUTENOLIDES

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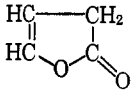
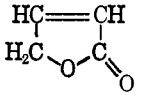
I. INTRODUCTION

Butenolides are unsaturated γ-lactones which may also be regarded as furan derivatives—2,3- and 2,5-dihydrofuran-2-ones (I and II). Compounds of this type are also known as crotonolactones. An interesting class of butenolides is that which constitutes the "E"

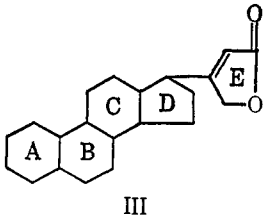


I



II

ring of naturally occurring steroids (III). Many of these steroidal lactones also exist in plants as glycosides.

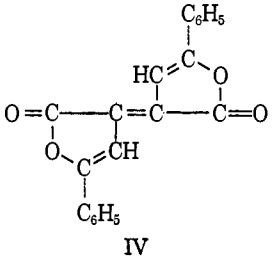


III

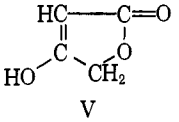
In either form, they exert a specific and powerful action on the cardiac muscle of humans and animals and, therefore, are known as cardenolides. A brief survey of these cardiac glycosides will be made later. Much of the current knowledge on butenolides was obtained from studies on complex molecules such as the cardenolides and other naturally occurring γ-lactones.

II. SCOPE OF THE REVIEW

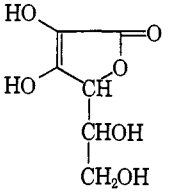
This review includes the chemistry of the $\Delta^{\beta,\gamma}$-butenolides and their $\Delta^{\alpha,\beta}$ isomers, the α-arylidene (or alkylidene) derivatives of the $\Delta^{\beta,\gamma}$ compounds, and γ-alkylidene (or arylidene) derivatives of the $\Delta^{\alpha,\beta}$-butenolides. A very brief survey of aglycons, such as strophanthidin, is also included. The chemistry of "Pechmann dyes" (IV), tetronic acids (V), and ascorbic acid (VI) will not be discussed since they have been reviewed elsewhere (118, 119, 143, 164, 165, 177, 188, 201, 233). Compounds not included in the discussion



IV



V

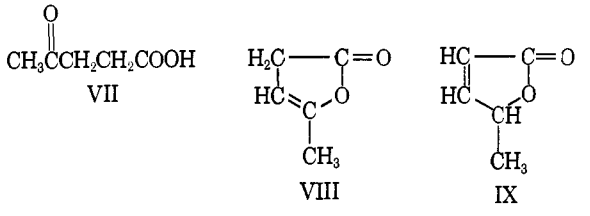


VI

are 3-oxo-2,3-dihydrofuran derivatives, which are isomeric with butenolides (67, 74, 128, 222, 223), and maleic anhydride, which may be considered as γ-oxo-$\Delta^{\alpha,\beta}$-butenolide.

III. NOMENCLATURE

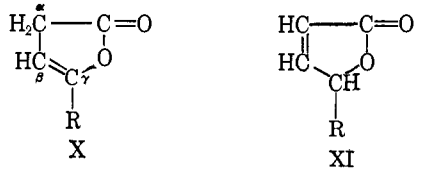
Much confusion exists in the nomenclature of these γ-lactones. Thus, for many years, butenolides have been called crotonolactones. Whether a given "crotonolactone" is an α,β or a β,γ isomer is usually indicated by specifying the position of the double bond by numbers or Greek letters. The term "isocrotonolactone" was used for the $\Delta^{\beta,\gamma}$ isomer (281), but more recently this usage has been applied to the $\Delta^{\alpha,\beta}$ isomer (269). The name "crotolactone" has also been employed by some authors to designate the $\Delta^{\beta,\gamma}$ isomers (180, 181). The lactones derived from levulinic acid (VII) are known as α-angelica lactone (VIII), the $\Delta^{\beta,\gamma}$ isomer, and β-angelica lactone (IX), the $\Delta^{\alpha,\beta}$ isomer.



VII VIII IX

The next higher homolog of VIII has been called "homoangelica lactone" (189, 191, 344), and the lactone obtained from δ-phenyllevulinic acid was called "phenyl angelica lactone," not to be confused with β-phenyl-α-angelica lactone. The term "butenolactone" has also been used recently (144, 324) to describe the $\Delta^{\alpha,\beta}$ isomer. In order to avoid all of this confusion, *Chemical Abstracts* names lactones after the hydroxycarboxylic acid from which they are derived. Thus, α-angelica lactone (VIII) is "4-hydroxy-3-pentenoic acid γ-lactone" and β-angelica lactone (IX) is "4-hydroxy-2-pentenoic acid γ-lactone." However, many authors continue to use the more common nomenclature for compounds VIII and IX.

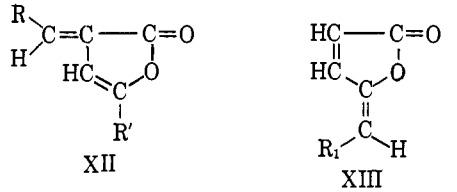
The butenolide nomenclature has found application in connection with work on cardiac glycosides (286) and was later suggested (104) in renaming α-benzal-γ-phenyl crotonolactone. In this review, the term butenolide will include crotonolactones and butenolactones, and the following system of numbering will be used throughout.



X XI

$\Delta^{\beta,\gamma}$-butenolide or Δ^{2}-butenolide

$\Delta^{\alpha,\beta}$-butenolide or Δ^{1}-butenolide



XII XIII

α-arylidene(or alkylidene)-γ-aryl(or alkyl)-$\Delta^{\beta,\gamma}$-butenolide

γ-arylidene(alkylidene)-$\Delta^{\alpha,\beta}$-butenolide

IV. METHODS OF PREPARATION

A. SYNTHESIS OF $\Delta^{\beta,\gamma}$-BUTENOLIDES

1. From γ-Keto Acids

γ-Keto acids (151), such as levulinic acid, which can enolize readily, give $\Delta^{\beta,\gamma}$-butenolides on slow distillation (125, 333, 335, 336, 354). This method has been applied to the synthesis of α-angelica lactone and β-ethyl-α-angelica lactone. The cyclization can also be effected by heating with acetic anhydride (376), acetyl chloride (69, 190), or with an acetic anhydride–sulfuric acid mixture.

A number of γ-aryl-$\Delta^{\beta,\gamma}$-butenolides have been prepared recently by acetic anhydride cyclization of β-aroylpropionic acids (328, 376).

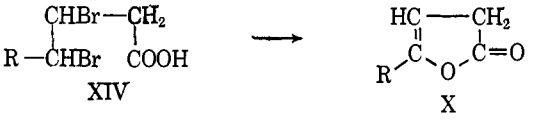
The conversion of levulinic acid to α-angelica lactone on a large scale has been achieved by heating with *p*-toluenesulfonic acid and ketene (153, 154) or by slow distillation under vacuum (203).

2. From Hydroxylactones

When aromatic aldehydes such as *p*-isopropylbenzaldehyde, piperonal (86, 87, 89), and anisaldehyde, react with phenylpyruvic acid, hydroxylactones are obtained. These compounds are converted to $\Delta^{\beta,\gamma}$-butenolides *via* the intermediate γ-keto acids.

3. From β,γ-Dibromo Acids

β,γ-Dibromo acids (XIV) on boiling with water or sodium carbonate solution (161, 191, 204), undergo hydrolysis and dehydrobromination to give $\Delta^{\beta,\gamma}$-butenolides. Thermal decomposition of XIV in the

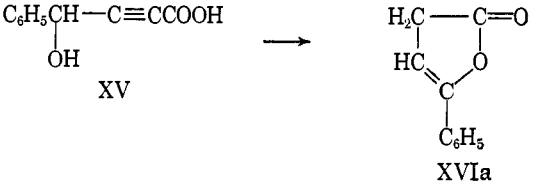


XIV X

presence of quinoline also led to the formation of $\Delta^{\beta,\gamma}$-butenolides (19).

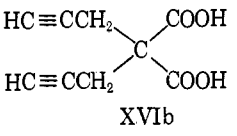
4. From Acetylenic Compounds

When the acetylenic acid XV is hydrogenated (243), γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (XVIa) is obtained.

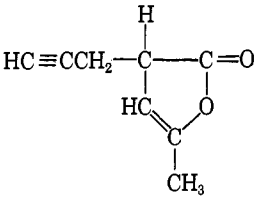


XV XVIa

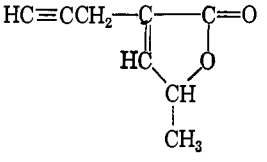
It has been shown recently that the acetylenic acid XVIb, when heated with zinc carbonate (302, 304, 306), forms α-propargyl-α-angelica lactone (XVII), α-propargyl-β-angelica lactone (XVIII), and bis(α-angelica lactone)-α,α'-spiran (XIX). Compound XVII



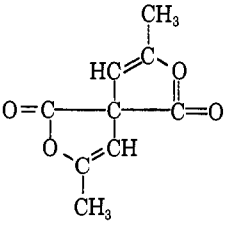
XVIb



XVII



XVIII

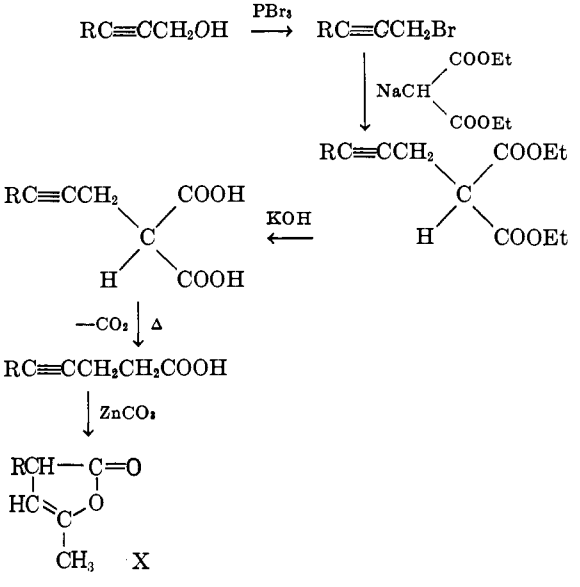


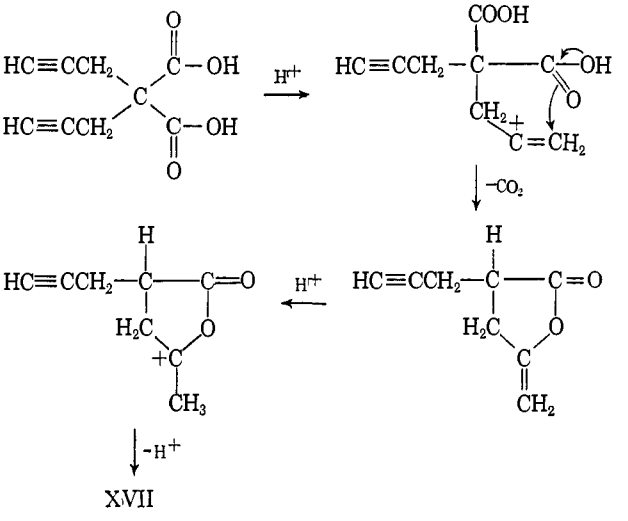
XIX

gave α-allyl-α-angelica lactone on reduction with Lindlar catalyst in methanol.

This conversion constitutes a general method as shown below. It has been found that with saturated aliphatic, allyl, or furylidene groups, the products are $\Delta^{\beta,\gamma}$-butenolides. With phenyl or propargyl substituents, α,β compounds are obtained (303).

The mechanism of conversion of dipropargylmalonic acid to XVII may proceed as follows.

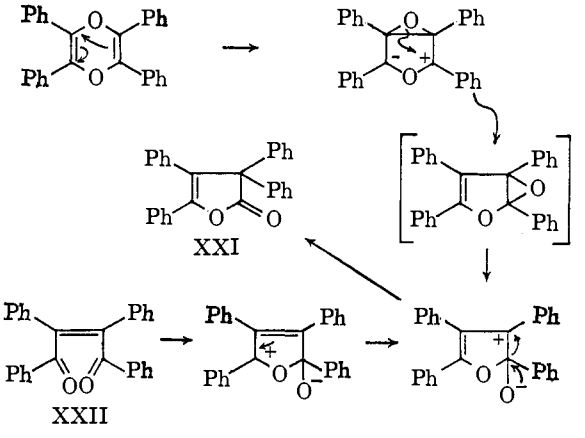




XVII

5. *Thermal Rearrangement*

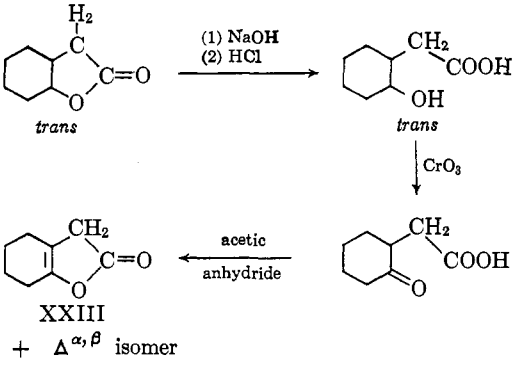
Tetraphenyl-*p*-oxadiene (XX), on heating with acetic, anhydride, gave $\alpha,\alpha,\beta,\gamma$-tetraphenyl-$\Delta^{\beta,\gamma}$-butenolide (XXI) (21). The lactone was also obtained from benzoin as follows. Benzoin was heated with *p*-toluenesulfonic acid in hexane, and water was distilled off azeotropically to give tetraphenylfuran, which was converted to *cis*-dibenzoylstilbene (XXII) by chromium trioxide oxidation. Pyrolysis of XXII gave the lactone XXI. The following mechanism was suggested for the thermal rearrangements.



XXI

XXII

6. *Condensed $\Delta^{\beta,\gamma}$-Butenolides*



XXIII

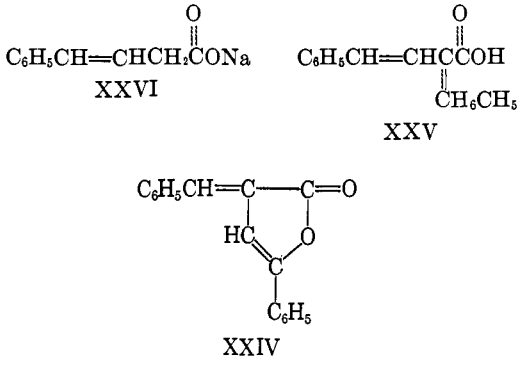
+ $\Delta^{\alpha,\beta}$ isomer

A $\Delta^{\beta,\gamma}$-butenolide with a cyclohexane ring fused in the β,γ-position has been reported (189, 242). Structural studies on ψ-santonin resulted in its subsequent synthesis (58).

The $\Delta^{\beta,\gamma}$-butenolides, prepared by the above methods, are listed in Table I.

B. α-ARYLIDENE-γ-ARYL- (OR ALKYL-) $\Delta^{\beta,\gamma}$-BUTENOLIDES

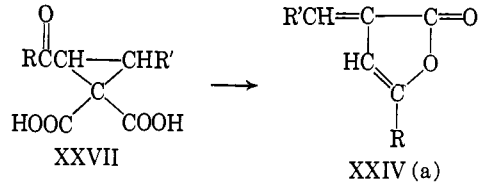
The earliest reported synthesis of α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (XXIV) was from dibenzylidenepropionic acid (XXV) (332, 333). Compound XXV was prepared by heating sodium phenylisocrotonate (XXVI) with benzaldehyde and acetic anhydride. This compound was treated with bromine in chloroform to give XXIV.



XXVI XXV XXIV

1. *Preparation from Cyclopropanecarboxylic Acids*

When compounds such as 2-phenyl-3-benzoylcyclopropanedicarboxylic acid (XXVII) are heated to 175°, rearrangement occurs with the formation of α-arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides along with β-aroylpropionic acids (180, 181, 183). Compound XXVII gave the two geometric isomers (180).



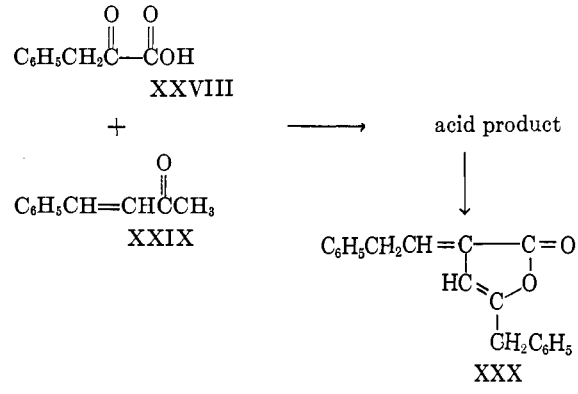
XXVII XXIV (a)

R′ = R = C_6H_5
R′ = 3-$NO_2C_6H_5$; R = C_6H_5
R′ = 3-Br-4-$CH_3OC_6H_3$; R = C_6H_5
R′ = C_6H_5; R = 4-BrC_6H_4

The conversion of XXVII to XXIV can also be effected by the action of hydrobromic acid in glacial acetic acid (180). However, these methods are not useful for the preparation of α-arylidenebutenolides.

2. *From Phenylpyruvic Acid*

The acid product, obtained by condensation of XXVIII with α,β-unsaturated ketones (XXIX) cyclizes in the presence of acetic acid and hydrochloric acid to give butenolide XXX (187).

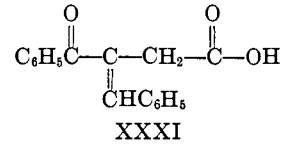


XXVIII XXIX XXX

3. *From γ-Keto Acids*

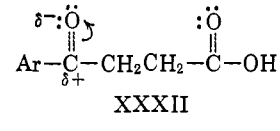
a. α-Arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides

The condensation of the sodium salt of β-benzoylpropionic acid with aromatic aldehydes in the presence of acetic anhydride gives α-arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides. This appears to be a satisfactory general method for the synthesis of these compounds (30, 31, 135, 139, 150). Instead of aromatic aldehydes, phthalic anhydride may be used to give the corresponding phthalidenebutenolides (31, 318). It was observed that when ethyl β-benzoylpropionate was treated with benzaldehyde in the presence of sodium ethoxide, β-benzoyl-β-benzylidenepropionic acid (XXXI) was



XXXI

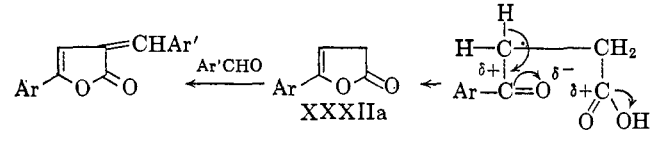
obtained (30). It has been pointed out (284) that in a β-aroylpropionic acid (XXXII), the β-methylene group should be more reactive than the α-methylene group from theoretical considerations. As the nucleophilic



XXXII

character of the carbonyl carbon atom is greater than that of the carboxyl carbon, one would expect aldol condensations with aldehydes to occur predominantly in the β-position. In the presence of acetic anhydride, XXXII lactonizes to give XXXIIa.

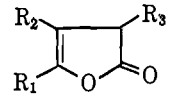
The α-methylene group, activated by the neighboring carboxyl group, condenses with aldehydes to give α-arylidene derivatives.



XXXIIa

TABLE I

$\Delta^{\beta,\gamma}$-BUTENOLIDES



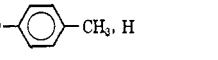
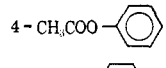
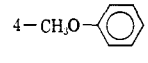
R_1 γ	R_2 β	R_3 α	Reference
C_6H_5	C_6H_5	H, H	90, 176, 332, 334
C_6H_5	H	$C_6H_5CH_2$, H	36, 332, 341
C_6H_5	C_6H_5	C_6H_5, C_6H_5	162
C_6H_5	H	$C_6H_5CH_2$, H	332, 337, 338
$C_6H_3O-CH_2-O$	C_6H_5	H, H	85, 87
CH_3	H	H, H	38, 40, 83, 100, 127, 145, 156, 157, 159, 343, 366
C_6H_5	H	H, H	114, 115, 190, 340
$C_6H_5CH_2$	H	H, H	111–113
p-*i*-PrC_6H_4	C_6H_5	H, H	88
p-$CH_3OC_6H_4$	C_6H_5	H, H	84, 89
C_2H_5	H	H, H	189
CH_3	CH_3	H, H	50, 160, 258
CH_3	H	CH_3, CH_3	159, 200, 259
H	CH_3	CH_3, CH_3	50, 160, 258
CH_3	CH_3	CH_3, CH_3	19, 50, 160, 258
CH_3	H	C_2H_5, H	345, 346
Br	Br	H, H	206
I	I	H, H	206
C_6H_5	H	C_6H_5, H	36, 243
C_6H_5	H	C_6H_5, H	281
C_6H_5	H	3,4-Di-$CH_3OC_6H_3$, H	281
C_6H_5	H	*p*-$CH_3OC_6H_4$, H	281
C_6H_5	OH	C_6H_5, H	184
C_6H_5	Br	C_6H_5, H	182
3,4-$(CH_3O)_2C_6H_3$	H	H, H	71, 135
p-Tolyl	H		47, 268
C_6H_5	Me	CH_3, C_6H_5	331
4-BrC_6H_4	H	H, H	354
4-$CH_3OC_6H_4$	H	H, H	354
CH_3	H	CH_3CO, H	171
	H	H, H	328
	H	H, H	328
2-Acetoxy 6-naphthyl	H	H, H	328
CH_3	$COOC_2H_5$	CH_3CO, H	25
CH_3	COOH	CH_3, H	35
CH_3	CH_3	OH, H	7
CH_3	CH_3	OH, COOH	7
H	Cl	H, H	132
H	C_6H_5NH	H, H	132
3-CH_3-4-$CH_3OC_6H_3$	H	H, H	376
2-CH_3-4-$CH_3OC_6H_3$	H	H, H	376
5-CH_3-2-$CH_3OC_6H_3$	H	H, H	376
2,4-$(CH_3O)_2C_6H_3$	H	H, H	376
o-$CH_3COOC_6H_4$	H	H, H	376
4-CH_3-2-$CH_3COOC_6H_3$	H	H, H	376
5-CH_3-2-$CH_3COOC_6H_3$	H	H, H	376
2,4-Di$CH_3COOC_6H_3$	H	H, H	376
p-$CH_3COOC_6H_4$	H	H, H	376
3-CH_3-4-$CH_3COOC_6H_3$	H	H, H	376
4-$CH_3OC_6H_4$	H	H, H	71
4-$CH_3C_6H_4$	H	H, H	71
p-$CH_3C_6H_4$	C_6H_5	H, H	16

TABLE I (*Continued*)

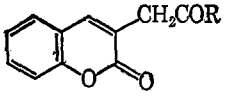
R_1 γ	R_2 β	R_3 α	Reference
p-$CH_3C_6H_4$	C_6H_5	H, $COCOOC_2H_5$	16
p-ClC_6H_4	C_6H_5	H, H	16
p-ClC_6H_4	p-$CH_3OC_6H_4$	H, H	16
C_6H_5	H	C_6H_5, H	15
4-$CH_3C_6H_4$	H	C_6H_5, H	15
4-ClC_6H_4	H	C_6H_5, H	15
4-ClC_6H_4	H	p-$CH_3OC_6H_4$, H	15
CH_3	H	Propargyl, H	61
CH_3	H	Allyl, H	61
C_6H_5	H	4-$CH_3OC_6H_4$, H	63
p-$CH_3OC_6H_4$	H	4-$C_6H_4OC_6H_4$, H	63
p-HOC_6H_4	H	C_6H_5, H	63
C_6H_5	C_6H_5	C_6H_5, C_6H_5	21
CH_3	H	C_2H_5, H	303
CH_3	H	Isobutyl, H	303
CH_3	H	Amyl, H	303
CH_3	H	n-C_8H_{17}, H	303
CH_3	H	Allyl, H	303
CH_3	H	Furfuryl, H	303
CH_3	H	C_6H_5, H	303
CH_3	H	$HC\equiv CCH_2$, H	303
CH_3	CH_3CO	CH_2, H	46
6-Methoxy-2-naphthyl	H	H, H	245
CH_3COO	CH_3	C_2H_5, C_2H_5OCO	234
CH_3	H	C_6H_5	93
CH_3	H	H, H	43
C_6H_5	H	C_6H_5, $C_{12}H_{25}$	369
$(CH_3)_3C$	H	$(CH_3)_3C$, H	363

The greater reactivity of β-methylene group is borne out by the observation that XXXII gave XXXI in the presence of sodium ethoxide. It has been suggested that in the condensation of aldehydes with β-aroylpropionic acids, γ-aryl-$\Delta^{\beta,\gamma}$-butenolides are intermediates, and this has been verified by the preparation of X and subsequent condensation with aldehydes (70, 71, 88).

A modification of this procedure is the use of the free β-aroylpropionic acid, rather than its salt. This variation has developed into the general method for preparing α-arylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides (70, 71, 104, 107–109, 134, 300, 318).

It has been observed that acetophenone, benzophenone, and other ketones fail to react under these conditions (105, 202). The yields of butenolides depend on the nature of the substituents on the aryl ring of the aldehydes. Electron-withdrawing substituents such as the nitro group give enhanced yields similar to the results obtained in the Perkin reaction.

A recent modification of the above method is the use of the dimethylformamide–sulfur trioxide complex in place of acetic anhydride–sodium acetate. The advantage of this variation is that hydroxybenzaldehydes, such as vanillin, give α-hydroxyarylidenebutenolides, rather than the α-acetoxy compound obtained by use of acetic anhydride. However, with DMF–SO_3, salicylaldehyde gives only a coumarin derivative XXXIII (18).

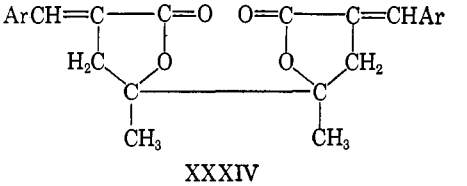


XXXIII

R=C_6H_5

b. α-Arylidene-γ-alkyl-$\Delta^{\beta,\gamma}$-butenolides

α-Angelica lactone (VIII) condenses with aromatic aldehydes to give arylidene derivatives (343). When sodium levulinate was condensed with aromatic aldehydes in the presence of acetic anhydride, poor yields of dimeric compounds XXXIV were obtained (32). These substances are hydrolyzed by alcoholic alkali to

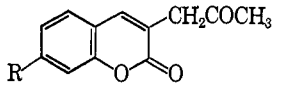


XXXIV

Ar = C_6H_5, p-$CH_3OC_6H_4$, 3,4-$(OCH_2O)C_6H_3$

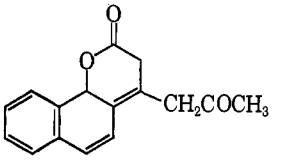
form α-arylidene levulinic acids. Hence, this method cannot be used for the preparation of γ-methyl-$\Delta^{\beta,\gamma}$-butenolides. α-Angelica lactone (VIII) was reported to react in the presence of diethylamine with a number of aromatic aldehydes, including salicylaldehyde, to give α-arylidene derivatives (249). However, the products obtained from salicylaldehyde, 2,4-dihydroxybenzaldehyde, and α-hydroxy-β-naphthaldehyde have

since been shown to be coumarin derivatives (XXXV and XXXVI) (226).



R=H, OH

XXXV

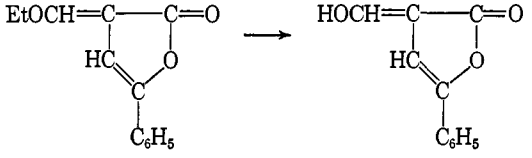


XXXVI

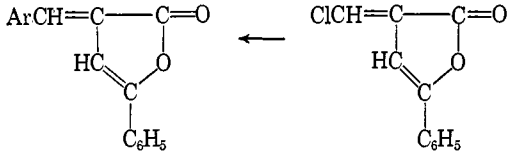
Condensations of α-angelica lactone with furfural derivatives and hydroxybenzaldehydes in the presence of amines give α-arylidene derivatives of VIII (226, 289). Triethylamine was also used recently in the condensation of VIII with aromatic aldehydes (372). It was observed that *m*-nitrobenzaldehyde gave low yields of α-*m*-nitrobenzylidene-α-angelica lactone, showing that aldehydes with electron-withdrawing groups diminish the yields. When α-angelica lactone reacts with formaldehyde, 3,5,5-tris(hydroxymethyl)dihydrodeoxypatulinic acid lactone (XXXVII) is obtained (250).

4. From α-Chloromethylene-γ-phenyl-Δ$^{\beta,\gamma}$-butenolide (XXXVIII)

β-Benzoylpropionic acid condenses with ethylorthoformate to give α-ethoxymethylene-γ-phenyl-Δ$^{\beta,\gamma}$-butenolide (XXXIX) which is converted to XXXVIII *via* its hydroxy analog XL (276). Compound XXXVIII, a vinylogous acid halide, reacts with benzene and chlorobenzene in the presence of anhydrous aluminum chloride and its α-*p*-chlorobenzylidene analog. Compound XXXVIII also reacts with aryl Grignard reagents to give α-arylidenebutenolides in high yields.



XXXIX XL

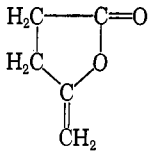


XXXVIII

Compounds prepared by all the above methods are listed in Table II.

C. Δ-$^{\alpha,\beta}$BUTENOLIDES

These compounds are considered to be the stable isomers. Several methods have been developed to prepare these compounds. The first Δ$^{\alpha,\beta}$-butenolide reported was β-angelica lactone (366). It was first thought to be a saturated compound with an exocyclic double bond in the γ-position. Later work revealed that the double bond was endocyclic with the butenolide, having the structure IX (335).



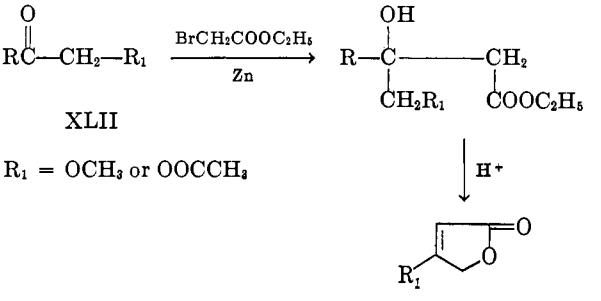
XLI

1. From Δ$^{\beta,\gamma}$-Butenolides

By the action of bases such as triethylamine, piperidine, and even benzylamine, Δ$^{\beta,\gamma}$-butenolides are converted to their Δ$^{\alpha,\beta}$ isomers (109, 335, 366). Acetic anhydride has also been employed to effect this isomerization. On a large scale, α-angelica lactone is converted to β-angelica lactone by passing its vapors over Fuller's earth (350).

2. The Reformatsky Reaction Route

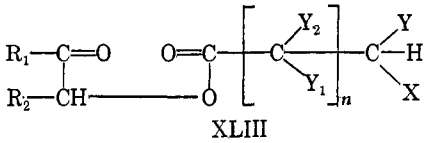
This is one of the most common methods for the synthesis of Δ$^{\alpha,\beta}$-butenolides and steroidal lactones. The only variation from the conventional procedure is the use of α-methoxy or acetoxy ketones (XLII) as the starting material. This route has been utilized by numerous investigators (22–24, 121, 137, 146, 178, 179, 208, 227, 252, 261–264, 286, 291–295, 325, 327, 347). The acetoxy derivative is usually obtained by treating the corresponding acid chloride with diazomethane. Esters (7) or ketones (172, 193) may also be used as starting materials. The conversion of the hydroxy ester to Δ$^{\alpha,\beta}$-butenolide is accomplished by heating in the presence of the acid sulfate of an alkali metal, anhydrous oxalic acid, or potassium dihydrogen phosphate (76).



XLII

R_1 = OCH_3 or $OOCCH_3$

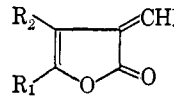
A modification to the above method is the so-called intramolecular Reformatsky reaction, which consists of heating a compound with zinc or magnesium metal in an inert solvent. Since compound XLIII is itself

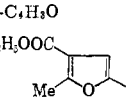
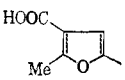


XLIII

R_1, R_2 = H or organic radical; X = halogen; Y_1, Y_2, Y_3 = H or alkyl; n = 0 or 1

TABLE II: $\Delta^{\beta,\gamma}$-BUTENOLIDES (α-ARYLIDENE OR ALKYLIDENE)



R_1 γ	R_2 β	R α	Reference
CH_3	CH_3	$C_6H_5CH{=}CH$	332
C_6H_5	H	C_6H_5	30, 33, 70, 104-106, 108, 202, 300, 332, 333
C_6H_5	CH_3	C_6H_5	333
C_6H_3-O-CH_2-O	C_6H_5	C_6H_5	86
C_6H_5	C_6H_5	C_6H_5	341
CH_3	H	p-$CH_3OC_6H_4$	35, 249, 343
p-i-PrC_6H_4	C_6H_5	C_6H_5	88
p-$CH_3OC_6H_4$	C_6H_5	C_6H_5	84, 89
β-$C_{10}H_7$	H	C_6H_5	35
C_6H_5	H	p-$CH_3OC_6H_4$	18, 30, 105, 303
C_6H_4	H	$C_6H_5CH{=}CH$	30
p-$CH_3C_6H_4$	H	C_6H_5	30
CH_3	H	$C_6H_5CH{=}CH$	30
C_6H_5	H	Phthalidene	31
p-$CH_3C_6H_4$	H	Phthalidene	31
CH_3	H	Phthalidene	31
p-$CH_3C_6H_4CH{=}CH$	H	Phthalidene	31
Piperonylidene	H	Piperonylidene	32
$C_6H_5CH{=}CH$	H	p-$CH_3OC_6H_4$	32
C_6H_5	H	m-$NO_2C_6H_4$	18, 71, 105, 183, 202, 300,
C_6H_5	H	3-Br-4-$CH_3OC_6H_3$	181
4-BrC_6H_4	H	C_6H_5	183
CH_3	H	2-HOC_6H_4[a]	226, 249
CH_3	H	4-HO-3-$CH_3OC_6H_3$	249
CH_3	H	Piperonal	249
C_6H_5	H	3,4-$(CH_3O)_2C_6H_3$	150
p-$CH_3OC_6H_4$	H	C_6H_5	150
3,4-$(CH_3O)_2C_6H_3$	H	o-$NO_2C_6H_4$	135
3,4-$(CH_3O)_2C_6H_3$	H	6-Nitroveratryl	135
3,4-$(CH_3O)_2C_6H_3$	H	6-Nitropiperonyl	135
4-$CH_3OC_6H_4$	H	C_6H_5	33
4-$CH_3OC_6H_4$	H	4-$CH_3OC_6H_4$	33
3,4-$(CH_3O)_2C_6H_3$	H	C_6H_5	33
3,4-$(CH_3O)_2C_6H_3$	H	4-$CH_3OC_6H_4$	33
3,4-$(CH_3O)_2C_6H_3$	H	Piperonyl	33
C_2H_5	H	C_6H_5	45
C_2H_5	H	4[$(CH_3)_2N$]C_6H_4	45
C_2H_5	H	α-C_4H_3O	45
C_2H_5	H	C_2H_5O	45
CH_3	H	α-C_4H_3O	289
CH_3	H		289
CH_3	H		289
CH_3	H	$C_6H_5C_6H_4$	289
CH_3	H	m-HOC_6H_4	289
CH_3	H	3,4-$(HO)_2C_6H_3$	289
CH_3	H	p-$CH_3CONHC_6H_4$	289
CH_3	H	p-$NH_2C_6H_4$	289
CH_3	H	p-$HOOCCH_2CH_2CONHC_6H_4$	289
CH_3	H	p-Phenylsulfonamidophenyl	289
CH_3	H	$C_6H_5CH{=}CH$	289
CH_3	H	p-$CH_3CONHC_6H_4CH{=}CH$	289
C_6H_5	H	3- or 6-quinolyl	318
C_6H_5	H	3- or 6-nitrophthalyl	318
C_6H_4	H	4- or 5-nitrophthalyl	318
C_6H_3	H	2-$NO_2C_6H_4$	300
C_6H_4	H	2,6-$Cl_2C_6H_3$	300
C_6H_5	H	2-ClC_6H_4	18, 300
C_6H_5	H	3-$CH_3COOC_6H_4$	300
C_6H_5	H	2,3-$(CH_3O)_2C_6H_3$	300
C_6H_5	H	4-$CH_3COOC_6H_4$	300
C_6H_5	H	4-$CH_3C_6H_4$	18, 300
C_6H_5	H	4-i-PrC_6H_4	18, 300

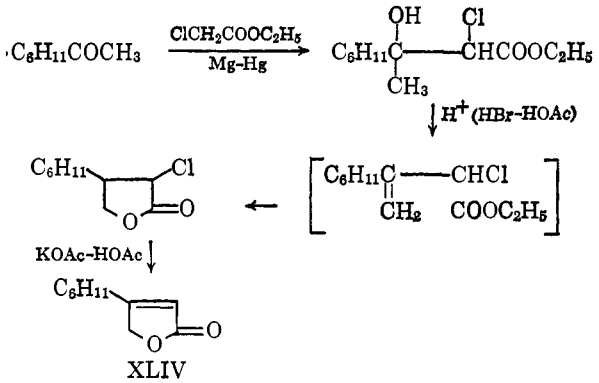
R_1 γ	R_2 β	R α	References
C_6H_5	H	4-CH_3COO-3-$CH_3OC_6H_3$	300
C_6H_5	H	3-Cl-4,5-di-$CH_3OC_6H_2$	300
C_6H_5	H	4-$CH_3OC_6H_4$	300
C_6H_5	H	α-Furfuryl	300
C_6H_5	H	4-$NO_2C_6H_4$	300
C_6H_5	H	3,4-(O-CH_2-O)-C_6H_3	300
C_6H_5	H	β-Phenylvinyl	300
C_6H_5	H	3,4-Di-$CH_3CH_2OC_6H_3$	300
C_6H_5	H	β-Furylvinyl	300
C_6H_5	H	4[$(CH_3)_2N$]C_6H_4	300
4-$CH_3C_6H_4$	H	C_6H_5	134
4-BrC_6H_4	H	C_6H_5	134
4-$CH_3OC_6H_4$	H	C_6H_5	134
4-ClC_6H_4	H	C_6H_5	134
3,4-Di-$CH_3C_6H_3$	H	C_6H_5	134
2-Tetralyl	H	C_6H_5	134
4-$C_6H_5OC_6H_4$	H	C_6H_5	134
4-$C_6H_5C_6H_4$	H	C_6H_5	134
4-$CH_3CONHC_6H_4$	H	C_6H_5	134
2-Thienyl	H	C_6H_5	134
3-Acenaphthyl	H	C_6H_5	134
2-Fluorenyl	H	C_6H_5	134
p-$CH_3OC_6H_4$	H	3,4-(O-CH_2-O)-C_6H_3	70
p-ClC_6H_4	H	3,4-Di-$CH_3OC_6H_3$	70
C_6H_5	H	3,4-Di-$CH_3OC_6H_3$	70
p-$CH_3C_6H_4$	H	3,4-(O-CH_2-O)C_6H_3	70
p-$CH_3OC_6H_4$	H	3,4-$(CH_3O)_2C_6H_3$	70
p-$CH_3C_6H_4$	H	3,4-$(CH_3O)_2C_6H_3$	70
p-$CH_3OC_6H_4$	H	m-$CH_3OC_6H_4$	70
C_6H_5	H	4-$CH_3OC_6H_4$	70
p-$CH_3OC_6H_4$	H	C_6H_5	70
CH_3	H	4[$(CH_3)_2N$]C_6H_4	372
CH_3	H	3,4-$(CH_3O)_2C_6H_3$	372
CH_3	H	3,4-$(C_2H_5O)_2C_6H_3$	372
CH_3	H	3-$NO_2C_6H_4$	372
$C_6H_5CH_2$	H	$C_6H_5CH_2$	187
$C_6H_5CH_2$	H	4-$CH_3C_6H_5CH_2$	187
C_6H_5	H	4-ClC_6H_4	18, 105, 202
C_6H_5	H	2,4-Di-ClC_6H_3	18
C_6H_5	H	3,4-Di-ClC_6H_3	18
C_6H_5	H	3-CH_3O-4-HOC_6H_2	18
C_6H_5	H	3,4-Di$MeOC_6H_3$	18
C_6H_5	H	$C_6H_5CH{=}CH$	18, 105, 202
C_6H_5	H	9-Fluorenyl	18
C_6H_5	H	2-HOC_6H_4[a]	18
C_6H_5	H	2-$CH_3OC_6H_4$	105, 202
C_6H_5	H	p-$NO_2C_6H_4$	105, 202
C_6H_5	H	α-$C_{10}H_7$	105, 202
C_6H_5	H	2-Furylidene	105, 202
C_6H_3	H	2-Thienylidene	105, 202
p-$CH_3OC_6H_4$	H	C_6H_5	71
p-$CH_3OC_6H_4$	H	2-$CH_3OC_6H_4$	71
p-$CH_3OC_6H_4$	H	3-$CH_3OC_6H_4$	71
p-$CH_3OC_6H_4$	H	4-$CH_3OC_6H_4$	71
p-$CH_3OC_6H_4$	H	3,4-$(CH_3O)_2C_6H_4$	71
p-$CH_3OC_6H_4$	H	C_6H_3(O-CH_2-O)	71
p-$CH_3C_6H_4$	H	3,4-$(CH_3O)_2C_6H_3$	71
p-$CH_3C_6H_4$	H	C_6H_3(O-CH_2-O)	71
p-$CH_3C_6H_4$	H	C_6H_5	71
3,4-Di-$CH_3OC_6H_3$	H	3,4-Di-$CH_3OC_6H_3$	71
3,4-Di-$CH_3OC_6H_3$	H	C_6H_3(O-CH_2-O)	71
3,4-Di-$CH_3OC_6H_3$	H	3-$CH_3OC_6H_4$	71
C_6H_4	H	3-$CH_3OC_6H_4$	71
p-ClC_6H_4	H	3-$CH_3OC_6H_4$	71
p-$CH_3C_6H_4$	H	3-$CH_3OC_6H_4$	71
2-$CH_3OC_6H_4$	H	3-$CH_3OC_6H_4$	71
p-Cl	H	C_6H_3(O-CH_2-O)	71
C_6H_5	H	C_6H_3(O-CH_2-O)	71
C_6H_4	H	3-ClC_6H_4	107
C_6H_5	H	3-BrC_6H_4	277
C_6H_5	H	$C_6H_5NHN{=}$	240
C_6H_5	H	p-$CH_3C_6H_4NHN{=}$	240
C_6H_5	H	p-$ClC_6H_4NHN{=}$	240
C_6H_5	H	m-$ClC_6H_4NHN{=}$	240
CH_3	H	$C_6H_5NHN{=}$	240

[a] These compounds are actually coumarins.

prepared from a ketone by a Reformatsky reaction, the advantage of this method seems to be the avoidance of excess bromoacetic ester which has deleterious effects on the product (290).

3. *Variation of Darzens Method*

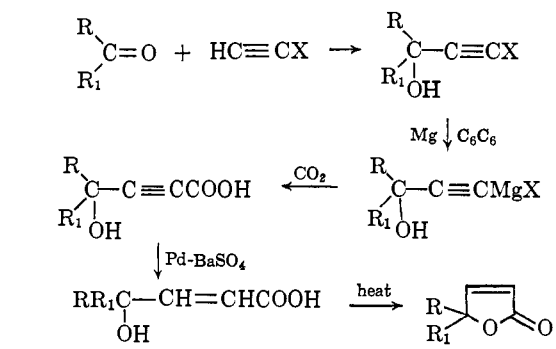
A variation of the Darzens glycidic ester synthesis leads to the formation of a $\Delta^{\alpha,\beta}$-butenolide. β-Cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (XLIV) was prepared by this method (26, 75).



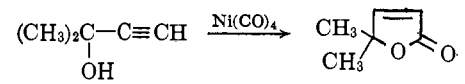
XLIV

4. *From Acetylenic Compounds*

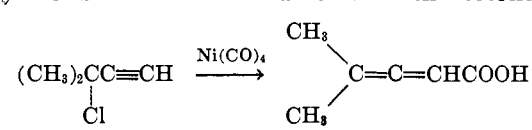
Acetylene carboxylic acids are obtained by treating the corresponding Grignard reagents with carbon dioxide. These acids are selectively reduced to give the ethylenic acids, which on heating cyclize to give $\Delta^{\alpha,\beta}$-butenolides (142, 317).



In a variation of this method, the acetylenic carbinol is converted directly to the butenolide by heating with nickel carbonyl in butyl alcohol and hydrochloric acid (166). It has been suggested that the reaction pro-

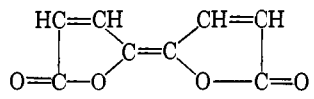


ceeds *via* an allenic carboxylic acid (XLV). Similarly, acetylene is heated in an autoclave with acetone and



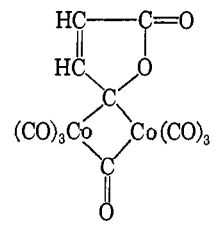
XLV

acetic anhydride at 100° and 250 atm. in the presence of dicobalt octacarbonyl to give octatrienediolide (XLVI) as the principal product (2). The complex



XLVI

of butenolide and cobalt carbonyl (XLVII) was also isolated (144, 324).



XLVII

When dipropargylmalonic acid was heated with zinc carbonate, α-propargyl-β-angelica lactone was isolated as one of the products (304). It was pointed out that phenyl and propargyl substituents on the malonic acid lead to formation of $\Delta^{\alpha,\beta}$-butenolides (303).

5. *From γ-Butyrolactones*

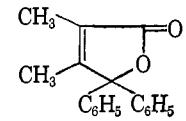
Saturated lactones with a substituent X in the α- or γ-position (where X = OH, $OOCCH_3$, SH, or NH_2), when treated with acids, acid salts, or substances which decrease surface tension, lose a molecule of HX to give a mixture of $\Delta^{\beta,\gamma}$- and $\Delta^{\alpha,\beta}$-butenolides. Treatment with base ensures a pure $\Delta^{\alpha,\beta}$ product (219, 297).

α-Chloro-β-cyclohexylbutyrolactone is converted to β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide by the action of potassium acetate in acetic acid (26, 75).

β-Formylpropionic acid derivatives with substituents on the α- or β-carbon atoms from γ-acetoxybutyrolactone compounds on heating with acetic anhydride. These lactones are dehydrated readily. Compounds with α- and β-substituents usually give $\Delta^{\alpha,\beta}$-butenolides and not the $\Delta^{\beta,\gamma}$ isomers (328). β-Bromo-β-aroylacrylic acids were shown to exist in the cyclic form (374, 375). Similarly, a solution of 2-phenyl-3-benzoylacrylic acid contains 70% α,γ-diphenyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide (44).

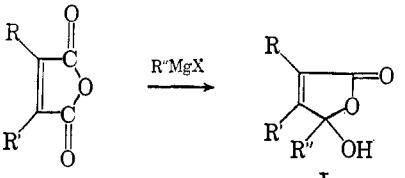
6. *From Substituted Maleic Anhydrides*

The reaction of phenyllithium with dimethylmaleic anhydride provides α,β-dimethyl-γ,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide (XLVIII) (331). Mono- and dialkylmaleic



XLVIII

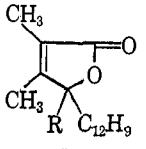
anhydrides (XLIX) react with alkylmagnesium or aralkylmagnesium halides at low temperature to give products which yield γ-hydroxy-γ-alkyl-$\Delta^{\alpha,\gamma}$-butenolides when decomposed with water.



XLIX L

These compounds can be further dehydrated to γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides (349). The latter compounds are used as antioxidants, flavoring agents, and sequestering agents for heavy metal ions.

When dimethylmaleic anhydride is subjected to a Friedel–Crafts reaction with biphenyl in carbon disulfide, α,β-dimethyl-γ,γ-dixenyl-$\Delta^{\alpha,\beta}$-butenolide and *cis*-2,3-dimethyl-3-*p*-xenoylacrylic acid are obtained (221). Compound LI is usually in the form of the cyclic compound, α,β-dimethyl-γ-hydroxy-γ-xenoyl-$\Delta^{\alpha,\beta}$-butenolide. Compound LI reacts with methanol and sulfuric acid to give the γ-methoxy analog; with hydrobromic acid, the γ-bromo compound forms.

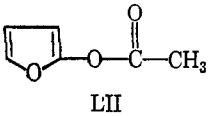


LI

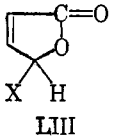
R=OH, Br, OCH_3

7. *From Furan Derivatives*

2-Acetoxyfuran (LII) reacts with bromine in carbon tetrachloride at low temperature to form γ-bromo-$\Delta^{\alpha,\beta}$-butenolide. The chloro and acetoxy analogs are obtained by treatment of LII with chlorine and lead tetraacetate, respectively (77).



LII

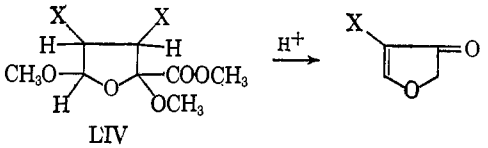


LIII

X=Br, Cl, $OCOCH_3$

8. *From Furoic Acid Derivatives*

α-Bromo-$\Delta^{\beta,\gamma}$-butenolide and its α-chloro analog are prepared by action of acid on 3,4-dihalo-2,5-dimethoxytetrahydrofuroic acid methyl ester (LIV) (138). This synthesis, together with dipole moment data for these compounds and their β-halo analogs



LIV

(326) helped to settle the controversy about the melting points of the α- and β-halo-$\Delta^{\alpha,\beta}$-butenolides (67, 126, 206, 239, 251, 362).

9. *From Substituted Acids*

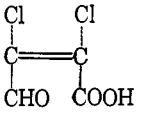
When 3,4-dihydroxybutyric acid lactone is heated with phosphorus pentoxide, $\Delta^{\alpha,\beta}$-butenolide II is obtained. Compound II is also prepared by heating 3,4-dichlorobutyric acid with aqueous sodium carbonate or methanolic sodium hydroxide (251).

10. *From α,β-Unsaturated Aliphatic Acids and Esters*

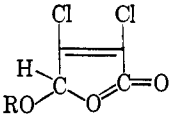
Treatment of ethyl crotonate with selenium dioxide or selenous acid causes the β-methyl group to be oxidized to an alcohol function. The resulting γ-hydroxy acid may be isolated as a γ-lactone (319).

11. *From Mucohalic Acids*

The esters of mucochloric acid exist in the form of cyclic compounds (236). Mucochloric acid condenses with acetophenone, nitromethane, or nitroethane in

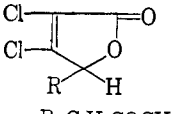


LV



LVI

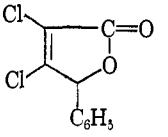
the presence of sodium hydroxide to provide γ-substituted α,β-dichloro-$\Delta^{\alpha,\beta}$-butenolides (237). Mucobromic acid reacts with acetophenone to give γ-phen-



R=$C_6H_5COCH_2$

acyl-α,β-dibromo-$\Delta^{\alpha,\beta}$-butenolide (353).

Mucochloric acid, when heated with benzene or chlorobenzene and anhydrous aluminum chloride, gives γ-phenyl-α,β-dichloro-$\Delta^{\alpha,\beta}$-butenolide (LVII) or its γ-*p*-chlorophenyl isomer. Compound LVII was



LVII

reported to react with methylamine to give γ-phenyl-β-chloro-α-methylamino-$\Delta^{\alpha,\beta}$-butenolide (96). However, a recent study (359) indicates that the β-chlorine atoms, and not the α-, are replaced in these reactions.

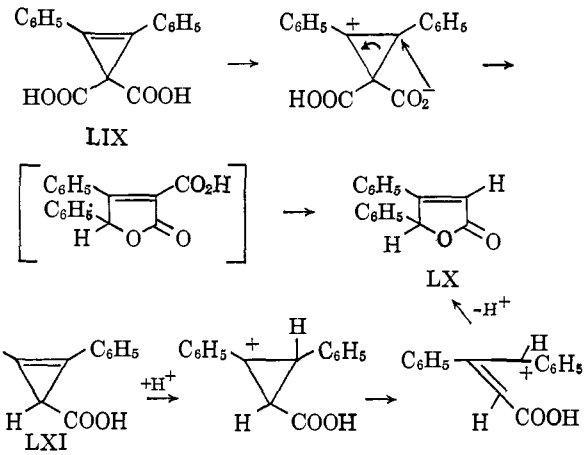
Mucochloric and mucobromic acids also react at room temperature with aromatic compounds (phenol, anisole) in the presence of polyphosphoric acid to give α,β-dihalo-$\Delta^{\alpha,\beta}$-butenolides. A number of compounds were prepared in this manner (307, 313).

12. From β-Formylacrylic Acids

α,β-Dihalo-β-formylacrylic acids (LVIII) condense with phenol, anisole, guaiacol, thymol, 1,2,3-trimethoxybenzene, and *o*-dimethoxybenzene in the presence of mineral acid to give γ-substituted $\Delta^{\alpha,\beta}$-butenolides (97, 307, 313).

13. From Cyclopropane Derivatives

Diphenylacetylene reacts with diazomalonic ester in the presence of copper dust to afford the ester of LIX. The free acid, 1,2-diphenylcyclopropene-3,3-dicarboxylic acid, gives, on thermal decomposition, β,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide (LX) (42a), also obtained from desylacetic acid (90, 334, 341). The conversion was also brought about by acid catalysts. Compound LX was also obtained from 1,2-diphenylcyclopropene-3-carboxylic acid (LXI) (42b). An ionic mechanism was suggested for the conversion.



LIX

LX

LXI

14. From α-Aryl-β-aroylpropionic Acids

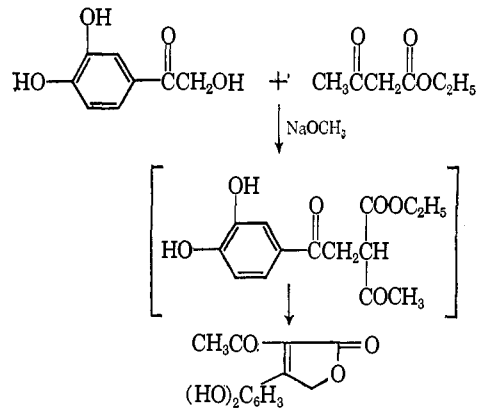
$\Delta^{\alpha,\beta}$-Butenolides are obtained when α-phenyl-β-benzoylpropionic acid and its analogs are heated with acetyl chloride (9), acetic anhydride, and sulfuric acid (16). These compounds have low melting points and their preparation is attended by formation of high melting substances, which were originally regarded to be $\Delta^{\beta,\gamma}$ isomers (62, 281). They have since been shown to be bislactones (268, 360, 363, 369). When the esters of these acids are treated with aromatic aldehydes in the presence of base, lactols are obtained. These lactols are γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolides (4–6).

15. Peracid Oxidation

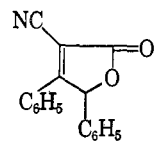
When 2,5-dimethylphenol is oxidized with peracetic acid, the product is α,α′-dimethyl-*cis*,*cis*-muconic acid, which, on heating in ethanol, gives γ-carbethoxy-α-methyl-$\Delta^{\alpha,\beta}$-butenolide (82).

16. From Ketonic Compounds

ω-Hydroxyacetophenones, which bear hydroxyl substituents on the aromatic ring, react with ethyl acetoacetate (sodium salt) in methanol to form $\Delta^{\alpha,\beta}$-butenolides (287, 314). This procedure has been extended to steroids (288). Similarly, acetophenone condensed with β-benzoylacrylic acid to form 2-methyl-



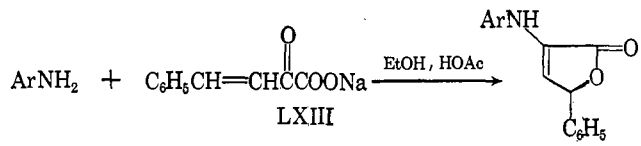
3,3-di(*p*-toluoyl)propionic acid, which gave a mixture of isomers when heated with acetic anhydride (47). Benzoin was condensed with cyanoethyl acetate to give α-cyano-β,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide (LXII).



LXII

17. From Pyruvic Acid Derivatives

Benzylidenepyruvic acid (LXIII) and aromatic amines react to form γ-aryl-α-arylamino-$\Delta^{\alpha,\beta}$-butenolides (LXIV). These compounds were originally



LXIII

LXIV

Ar = C_6H_5, *o*-$NO_2C_6H_4$, *p*-$CH_3C_6H_4$, 2-$C_{10}H_7$, *p*-$CH_3OC_6H_4$

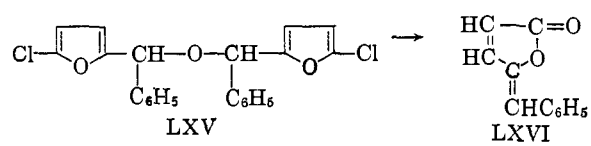
considered to be pyridinediones (220, 232, 352, 356). Pyruvic acid condenses with *o*-nitrobenzaldehyde to give α-hydroxy-γ-(*o*-nitrophenyl)-$\Delta^{\alpha,\beta}$-butenolide (323).

Compounds prepared by the above methods are given in Table III.

D. γ-ARYLIDENE- (OR ALKYLIDENE-) $\Delta^{\alpha,\beta}$-BUTENOLIDES

1. From Furan Derivatives

Bis(5-chlorofuryl-2-methylphenyl) ether (LXV) gives γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolide on reaction with concentrated sulfuric acid (125).

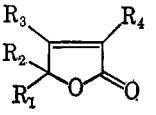


LXV

LXVI

TABLE III

$\Delta^{\alpha,\beta}$-BUTENOLIDES



R_1, R_2 γ	R_3 β	R_4 α	Reference
H, C_6H_5	C_6H_5	H	90, 332, 334, 341
H, CH_3	H	H	39, 366
H, C_6H_5	H	$C_6H_5CH_2$	332, 337
H, C_6H_5	H	C_6H_5CHBr	337
H, H	H	H	29, 101, 205
H, C_6H_5	C_6H_5	Br	341
H, C_6H_5	H	H	340
$C_6H_5CH_2$, H	H	C_6H_5	342
$C_6H_5CH_2$, H	H	H	344
H, C_6H_3(O–CH_2–O)-3,4	C_6H_5	H	87
p-$CH_3OC_6H_4$–, H	C_6H_5	H	84
H, H	Br	Br	206
H, H	I	I	206
H, H	H	Br	206
H, H	C_6H_5	H	85, 131
–CH_2COOH, –C_6H_4	–C_6H_4	H	24
–CH_2COOH, C_6H_5	C_6H_5	H	22, 23
–CHICOOH, C_6H_5	C_6H_5	H	22
H, C_6H_5	C_6H_5	H	36
H, OH	H	H	14, 99, 207, 229
Cl, C_6H_5	Br	Br	184
C_6H_5, C_6H_5	H	C_6H_5	373
H, C_6H_5	C_6H_5	CN	230
H, C_6H_5	HO	C_6H_5	184
CH_3, p-ClC_6H_4	H	C_6H_5	185
H, C_6H_5	H	C_6H_5	281
H, C_6H_5	H	p-$CH_3OC_6H_4$	281
H, C_6H_5	H	3,4-$(CH_3CH_2O)_2C_6H_3$	281
H, p-$CH_3C_6H_4$	H	p-$CH_3C_6H_4COCH_2$	268
H, C_6H_5	NH_2	NH_2	238
C_9H_{12}, C_9H_{12}	CH_3	CH_3	221
C_6H_5, C_6H_5	CH_3	CH_3	331
C_6H_5, C_6H_5	H	H	241
H, H	C_6H_5	H	26, 208, 228, 252, 286
H, H	C_6H_{13}	H	26, 75, 208, 286
H, H	C_5H_{11}	H	286
H, H	2-$C_{10}H_7$	H	208
H, H	1-$C_{10}H_7$	H	178
H, H	1-Hydroindanyl	H	178
H, H	6-CH_3O-2-$C_{10}H_6$	H	178
H, H	6-HO-2-$C_{10}H_6$	H	178
H, H	Decahydro-2-$C_{10}H_6$	H	178
H, H	Norcholanyl	H	179
H, H	p-Anisyl	H	227
H, H	p-$C_6H_5OC_6H_4$	H	73, 227
H, H	4-$CH_3COOC_6H_4$	H	227
H, H	3-HOC_6H_4	H	227
H, H	3-$CH_3OC_6H_4$	H	227
H, H	2-HOC_6H_4	H	227
H, H	2-$CH_3OC_6H_4$	H	227
H, H	2-ClC_6H_{13}	H	227
H, H	($3\alpha,7\alpha,12\beta$-Tri-OH-23-norcholanyl)	H	136
H, OH	H	CH_2=CH	78
H, CH_2COOH	CH_3	H	253
H, CH_3	H	CH_3	11
H, H	*trans*-4-Hydroxycyclohexyl	H	136
H, H	H	C_6H_5	328
H, H	H	p-Anisyl	328
H, H	H	α-Cyclohexyl	328
H, H	H	H	328
H, H	$C_6H_5CH_2$	H	262
H, H	*cis*-4-Hydroxycyclohexyl	H	134
H, H	$COOC_2H_5$	H	48
CH_3, CH_3	H	H	42
CH_3, H	H	H	42
CH_3, H	NH_2	NH_2	321
H, H	CH_3	HO	116
H, CH_3	H	HO	298
H, CH_3	CH_3	HO	298
H, H	CH_3	H	49, 117
H, H	3-Phenanthryl	H	172
H, H	2-Phenanthryl	H	172

TABLE III (*Continued*)

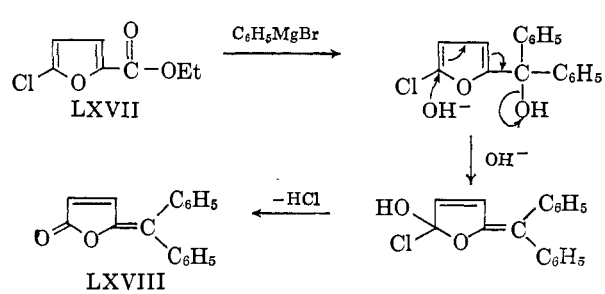
R_1, R_2 γ	R_3 β	R_4 α	Reference
H. $COOC_2H_5$	H	CH_3	82
H, CH_2COOCH_3	CH_3	H	81
H, H	H	CH_3	149
H, H	p-$C_3H_7C_6H_4$	H	80
CH_3, H	CH_3	CH_3CO	194
C_2H_5, H	C_2H_5	CH_3CO	194
$C_{11}H_{23}$, H	$C_{11}H_{23}$	CH_3CO	194
C_3H_7, H	C_3H_7	CH_3CO	194
C_6H_5, H	C_6H_5	CH_3CO	194
H, H	C_6H_5	CH_3CO	194
H, H	C_6H_5NH	H	132
H, H	CH_3	H	193
H, H	ω-CH_3COO-n-C_3H_6	H	193
H, H	ω-Phthalimido-n-propyl	H	193
H, H	OH	C_4H_9	28
H, H	OH	$C_6H_5CH_2$	28
C_6H_5, H	H	CH_3	274
2-$C_{10}H_7$, H	H	CH_3	273
C_6H_5, H	Br	Br	353
C_6H_5, H	CH_3O	H	243
C_6H_5, H	$(C_2H_5)_2N$	H	243
C_6H_5, H	HO	H	243
H, H	H	Br	251
H, H	CH_3	Br	171
H, H	Br	Br	68
H, Br	H	H	77, 175
C_6H_5, Cl	Cl	Cl	96
p-ClC_6H_4, Cl	Cl	Cl	96
Cl, H	H	H	77
CH_3COO, H	H	H	77
p-HOC_6H_4, H	Cl	Cl	97
p-$CH_3OC_6H_4$, H	Cl	Cl	97
3,4-$(CH_3O)_2C_6H_3$, H	Cl	Cl	97
2,3,4-$(CH_3O)_3C_6H_2$, H	Cl	Cl	97
3-CH_3O-4-HOC_6H_3, H	Cl	Cl	97
2-CH_3-4-HO-5-$C_3H_7C_6H_2$, H	Cl	Cl	97
$C_6H_5COCH_2$, H	Cl	Cl	236
$-CH_2NO_2$, H	Cl	Cl	236
CH_3CHNO_2, H	Cl	Cl	236
$(CH_3)_2CNO_2$, H	Cl	Cl	236
α-Cyanobenzyl, H	Cl	Cl	236
Carbamoylcyanoethyl, H	Cl	Cl	236
Cl, H	Cl	Cl	236
p-$CH_3OC_6H_4$, H	H	H	307
2,3,4-$(CH_3O)_3C_6H_2$, H	H	H	307
p-BrC_6H_4, H	Br	HO	322
CH_3O, H	Br	Cl	359
CH_3O, H	Cl	Cl	359
CH_3O, H	C_6H_5NH	Cl	359
CH_3O, H	C_6H_5NH	Br	359
C_6H_5, HO	H	C_6H_5	44
4-Hydroxy-1-naphthylimino, H	H	H	348
C_6H_5, OH	$C_6H_5CH_2$	C_6H_5	4
4-ClC_6H_4, OH	$C_6H_5CH_2$	C_6H_5	4
4-BrC_6H_4, OH	$C_6H_5CH_2$	C_6H_5	4
4-$CH_3OC_6H_4$, OH	$C_6H_5CH_2$	C_6H_5	4
C_6H_5, OH	2-$CH_3OC_6H_4CH_2$	4-$CH_3OC_6H_4$	4
4-ClC_6H_4, OH	C_6H_3(O–CH_2–O)	C_6H_5	4
C_6H_5, CH_3O	$C_6H_5CH_2$	C_6H_5	4
4-ClC_6H_4, CH_3O	$C_6H_5CH_2$	C_6H_5	4
4-BrC_6H_4, CH_3O	$C_6H_5CH_2$	C_6H_5	4
C_6H_5, CH_3CO	$C_6H_5CH_2$	C_6H_5	4
4-ClC_6H_4, CH_3CO	$C_6H_5CH_2$	C_6H_5	4
4-ClC_6H_4, CH_3COO	C_6H_2(O–CH_2–O)(–CH_2)	C_6H_5	4
H, H	p-Allyl-m-acetoxy	H	120
H, H	CH_3CONH	CH_3CO	120
H, H	CH_3	CH_3	1
C_6H_5, H	H	C_6H_5NH	357
H, H	3,4-$(HO)_2C_6H_3$	CH_3CO	287
H, H	3,4-$(HO)_2C_6H_3$	Butyroyl	287
H, H	3,4-$(HO)_2C_6H_3$	C_6H_5CO	287
H, H	3,4-$(HO)_2C_6H_3$	Caproyl	287
H, H	4-$CH_3OC_6H_4$	CH_3CO	287
H, H	4-BrC_6H_4	CH_3CO	287
H, H	3-$NO_2C_6H_4$	CH_3CO	287
H, H	3,4-Bisbenzyloxy-C_6H_3	CH_3CO	287
H, H	4-$CH_3CONHC_6H_5$	CH_3CO	287
C_6H_5, C_6H_5	H	H	163

TABLE III (*Continued*)

R_1, R_2 γ	R_3 β	R_4 α	Reference
C_6H_5, H	H	C_6H_5NH	232
CH_3, CH_3	H	H	166
H, *p*-$CH_3OC_6H_4$	H	*p*-$CH_3OC_6H_4NH$	63
H, *p*-$CH_3OC_6H_4$	H	C_6H_5	63
CF_3, H	H	H	129
CH_3, CH_3COO	CH_3	H	37
4-BrC_6H_4, $C_6H_5NCH_3$	CH_3	H	219
H, H	H	H	317
H, CH_3	C_6H_5	H	93
H, H	Br	Br	138
H, H	Cl	Cl	138
CH_3, CH_2OR[a]	H	H	320
HO, C_6H_5	CH_3O	H	375
HO, *p*-RC_6H_4	Br	H	375
CH_3O, *p*-RC_6H_4	Br	H	375
H, C_6H_5	H	$(C_6H_5)_2CH$	109
C_6H_5, H	H	C_6H_5NH	352
C_6H_5, H	H	*p*-$CH_3C_6H_4NH$	352
C_6H_5, H	H	2-$C_{10}H_7NH$	352
C_6H_5, H	H	*p*-$CH_3OC_6H_4NH$	352
p-$CH_3OC_6H_4$, H	H	*p*-$CH_3OC_6H_4NH$	352
2-$NO_2C_6H_4$, H	H	HO	254
C_2H_5, OH	CH_3	CH_3	349
C_3H_7, OH	CH_3	CH_3	349
C_4H_9, OH	CH_3	CH_3	349
C_5H_{11}, OH	CH_3	CH_3	349
C_6H_{13}, OH	CH_3	CH_3	349
C_7H_{15}, OH	CH_3	CH_3	349
3-$CH_3C_4H_8$, OH	CH_3	CH_3	349
1-$C_2H_5C_3H_6$, OH	CH_3	CH_3	349
Cyclohexyl, OH	CH_3	CH_3	349
Cyclohexylmethyl, OH	CH_3	CH_3	349
β-Phenylethyl, OH	CH_3	CH_3	349
$C_6H_5CH_2$, OH	CH_3	CH_3	349
C_4H_9, OH	C_2H_5	C_2H_5	349
n-C_5H_{11}, OH	C_2H_5	C_2H_5	349
n-C_6H_{13}, OH	C_2H_5	C_2H_5	349
n-C_5H_{11}, OH	C_4H_9	C_4H_9	349
n-C_5H_{11}, OH	H	CH_3	349
n-C_5H_{11}, OH	CH_3	H	349
4-HOC_6H_4, H	Br	Br	308
3,4-$(CH_3O)_2C_6H_2$, H	Br	Br	308
2,3,4-$(CH_3O)_3C_6H_2$, H	Br	Br	308
4-$C_2H_5OC_6H_4$, H	Cl	Cl	308
4-$C_3H_7OC_6H_4$, H	Cl	Cl	308
4-$C_4H_9OC_6H_4$, H	Cl	Cl	308
2,4,5-$(CH_3O)_3C_6H_2$, H	Cl	Cl	308
2,4,6-$(CH_3O)_3C_6H_2$, H	Cl	Cl	308
4-$CH_3SC_6H_4$, H	Cl	Cl	308
4-$CH_3OC_6H_4$, H	Cl	Br	308
2-$CH_3OC_{10}H_6$, H	Cl	Cl	308
4-$CH_3OC_{10}H_6$, H	Cl	Cl	308
2-$C_2H_5OC_{10}H_6$, H	Cl	Cl	308
4-$C_2H_5OC_{10}H_6$, H	Cl	Cl	308
4-$CH_3OC_6H_4$, H	Br	Cl	308
C_6H_5, H	Br	Br	308
4-$CH_3OC_6H_4$, H	Br	OH	308
4-$CH_3OC_6H_4$, H	Br	CH_3O	308
4-$CH_3OC_6H_4$, H	Cl	OH	308
4-$CH_3OC_6H_4$, H	Cl	CH_3O	308
4-$CH_3OC_6H_4$, H	Cl	Cl	308
C_6H_5, H	Cl	Cl	308
4-HOC_6H_4, H	Cl	Cl	308
C_6H_5, H	Br	Br	308
$(CH_3)_3C$, H	H	$(CH_3)_3C$	363
C_2H_5, $C_{12}H_{25}$	H	C_6H_5	369

[a] R = H or tetrahydropyranyl.

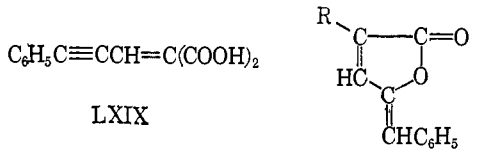
Ethyl 5-chloro-2-furoate (LXVII) and phenylmagnesium bromide reacted to form γ-diphenylmethylene-$\Delta^{\alpha,\beta}$-butenolide (LXVIII) (125). The mechanism suggested for the formation of LXVIII is shown.



2. *From Acetylene Derivatives*

Phenylpropargaldehyde reacts with malonic acid to furnish phenylpropargylidenemalonic acid (LXIX). When this compound is heated at 190°, γ-benzylidene-

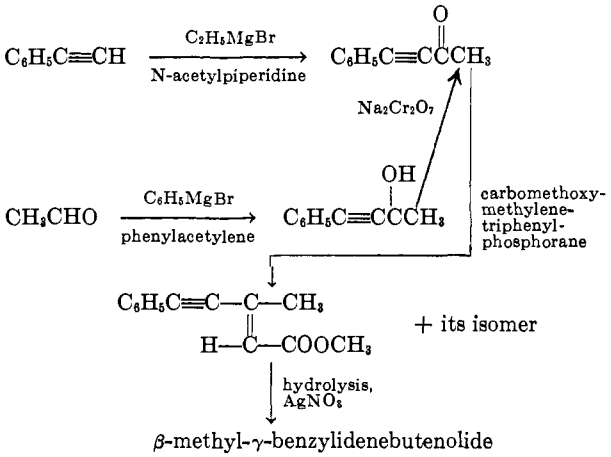
α-carboxybutenolide (LXX) is obtained. Decarboxylation of LXX at 250° yields γ-benzylidenebutenolide (LXXI) (51). Compounds LXX and LXXI were



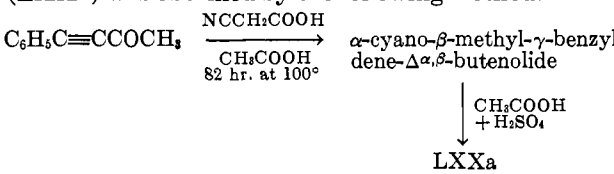
LXIX

LXX, R = COOH
LXXI, R = H

also made according to the following method from 4-phenyl-3-butyn-2-one (3).

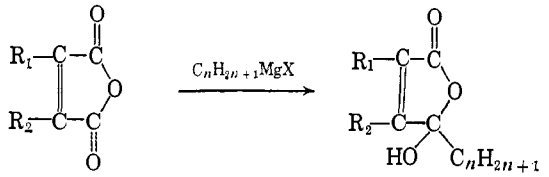


α-Carboxy-β-methyl-γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolide (LXXa) was obtained by the following method.



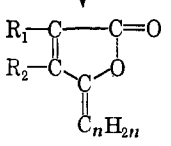
3. *From γ-Hydroxy-$\Delta^{\alpha,\beta}$-butenolides*

When monoalkylmaleic anhydrides or dialkylmaleic anhydrides are treated with Grignard reagents at low temperatures, di- or trisubstituted γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolides are obtained. Dehydration with a mixture of acetic anhydride, acetic acid, and sulfuric acid provides γ-alkylidene- (or arylidene-) $\Delta^{\alpha,\beta}$-butenolides (LXXII) (349).



XLIX

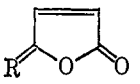
L



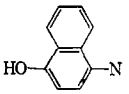
LXXII

Compounds prepared by the above methods are listed in Table IV.

TABLE IV



γ-ALKYLIDENE- (OR ARYLIDENE-) $\Delta^{\alpha,\beta}$-BUTENOLIDES

γ	α	β	Ref.
p-HOC_6H_4N	H	H	260
CH_3CH	H	H	45
CH_2	H	H	312
$(C_6H_5)_2C$	H	H	125
$(C_6H_5)_2C$	Br	H	125
C_6H_5CH	H	H	3, 51
C_6H_5CH	COOH	H	3, 51
C_6H_5CH	$COOCH_3$	CH_3	3
C_6H_5CH	CN	CH_3	3
p-$NO_2C_6H_4CH$	$COOCH_3$	CH_3	3
p-$CH_3C_6H_4CH$	$COOCH_3$	CH_3	3
p-ClC_6H_4CH	$COOCH_3$	CH_3	3
C_2H_4	CH_3	CH_3	349
C_3H_6	CH_3	CH_3	349
n-C_4H_8	CH_3	CH_3	349
n-C_5H_{10}	CH_3	CH_3	349
n-C_6H_{12}	CH_3	CH_3	349
n-C_7H_{14}	CH_3	CH_3	349
3-Methylbutylidene	CH_3	CH_3	349
1-Ethylpropylidene	CH_3	CH_3	349
Cyclohexylidene	CH_3	CH_3	349
Cyclohexylmethylene	CH_3	CH_3	349
β-Phenylethylidene	CH_3	CH_3	349
C_6H_5CH	CH_3	CH_3	349
n-C_4H_8	C_2H_5	C_2H_5	349
n-C_5H_{10}	C_2H_5	C_2H_5	349
n-C_6H_{12}	C_2H_5	C_2H_5	349
n-C_5H_{10}	*n*-C_4H_9	*n*-C_4H_9	349
n-C_5H_{10}	CH_3	H	349
n-C_5H_{10}	H	CH_3	349
C_6H_5CH	H	C_6H_5	339
	H	H	348
$HOCH_2CH$	H	$(CH_3O)_2CH$	311

V. PHYSICAL PROPERTIES

Alkyl-substituted butenolides having no exocyclic double bond are usually liquids. α-Arylidene-γ-aryl-(or alkyl)butenolides are usually solids with the color varying from yellow to brown. These compounds are fusible and do not decompose above their melting points. They are soluble in most organic solvents and are most frequently crystallized from ethanol.

VI. SPECTRAL PROPERTIES

Much research has been carried out on the infrared, ultraviolet, nuclear magnetic resonance, and mass spectra of butenolides.

A. INFRARED SPECTRA

$\Delta^{\beta,\gamma}$-Butenolides, such as α-angelica lactone, show carbonyl absorption at 1800–1795 cm.$^{-1}$ (45, 58, 62, 130, 256, 365). α,γ-Diaryl- and β,γ-diaryl-$\Delta^{\beta,\gamma}$-butenolides have been reported to show carbonyl bands in the 1770–30 cm.$^{-1}$ region (15, 63). In particular, the compound presumed to be α,γ-diphenyl-$\Delta^{\beta,\gamma}$-butenolide exhibits a band at 1763 cm.$^{-1}$ (63, 360, 369), but this compound has since been shown to be a bislactone (268, 360, 363, 369). The authentic α, γ-

diphenyl-$\Delta^{\beta,\gamma}$-butenolide (278, 281), however, shows carbonyl absorption at 1795 cm.$^{-1}$. This shift to higher frequencies from the absorption of saturated five-membered lactones (1770 cm.$^{-1}$) parallels the shift observed in open chain vinyl esters (279). The carbon–carbon double bond absorption is found at 1682 cm.$^{-1}$ (279). This has also been attributed to the >C=C—O grouping (283).

The $\Delta^{\alpha,\beta}$-butenolides show carbonyl absorption near 1750 cm.$^{-1}$ (45, 167–169, 273, 274, 304, 360, 369). A systematic study of the $\Delta^{\alpha,\beta}$-butenolides (8, 167–169) has been made. Most of these compounds showed a typical doublet carbonyl absorption at 1785 (band A) and 1745 cm.$^{-1}$ (band B). The intensity of band A is higher in carbon tetrachloride. In chloroform, the situation is reversed. Similar behavior is also observed in the spectra of steroidal lactones (168). The spectra of $\Delta^{\alpha,\beta}$-butenolides in carbon disulfide are similar to those in CCl_4, while the spectra of pure liquids are similar to those in chloroform. The intensities of these bands are not affected by changes in concentration, showing that association in solution has not taken place. At higher temperatures, the intensity of band A increased and that of band B decreased. The presence of two carbonyl bands may be due to Fermi resonance between the true carbonyl stretching vibration and a second vibration, possibly an overtone of a low frequency fundamental (168, 169). A correlation between the bond angle in a carbonyl compound (108° for $\Delta^{\alpha,\beta}$-butenolide) and the carbonyl frequency was examined recently (59).

The α-arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides show carbonyl absorption at 1787–1760 cm.$^{-1}$, depending on the nature of the substituent on the arylidene group (104, 105). The carbonyl absorption of α-arylidene-γ-alkyl-$\Delta^{\beta,\gamma}$-butenolides is reported to be at 1750 cm.$^{-1}$, showing that the nature of the substituent on the γ-carbon atom also influences the absorption (45). γ-Arylidene-$\Delta^{\alpha,\beta}$-butenolides exhibit bands at 1790 cm.$^{-1}$ (3, 51).

B. ULTRAVIOLET SPECTRA

α-Arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides show maxima at 260–300 and 395–410 mμ. The strong absorption at 410 mμ is attributed to the $C_6H_5CH{=}C{-}CH{=}CC_6H_5$ moiety (104, 134, 300). γ-Arylidene-$\Delta^{\alpha,\beta}$-butenolides show maxima at 224, 240, and 325 mμ (3, 51). $\Delta^{\alpha,\beta}$-Butenolides absorb at 220 mμ (26, 235, 370).

C. MISCELLANEOUS

The mass spectra of $\Delta^{\alpha,\beta}$-butenolide, β-angelica lactone, and α-angelica lactone were examined (122). The main peaks of the spectra result from splitting of two alternate bands of the lactone rings. The nuclear magnetic resonance spectrum of $\Delta^{\alpha,\beta}$-butenolide has been examined and the coupling constants measured (120, 361). The paper chromatographic R_f values of several $\Delta^{\alpha,\beta}$-butenolides have also been measured (224, 371).

VII. REACTIONS OF BUTENOLIDES

In general, $\Delta^{\beta,\gamma}$-butenolides behave as cyclic esters. α-Arylidene-$\Delta^{\beta,\gamma}$-butenolides show multicentered reactivity due to the additional structural feature of the α,β-unsaturated carbonyl system. $\Delta^{\alpha,\beta}$-Butenolides behave normally. Little or no information is available on the reactivity of the γ-arylidene-$\Delta^{\alpha,\beta}$-butenolides. The following sections will deal in detail with the reactions of butenolides.

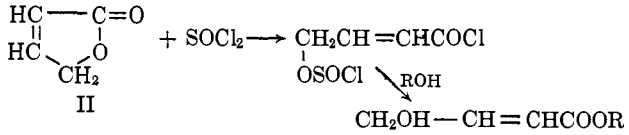
A. REACTION WITH ACIDS AND BASES

1. Reaction with Acids

$\Delta^{\beta,\gamma}$-Butenolides are hydrolyzed by sulfuric acid to give γ-keto acids (340). With α-arylidene-γ-arylbutenolides, however, the reaction with hydrochloric and acetic acids leads to the formation of naphthoic acids (70, 71).

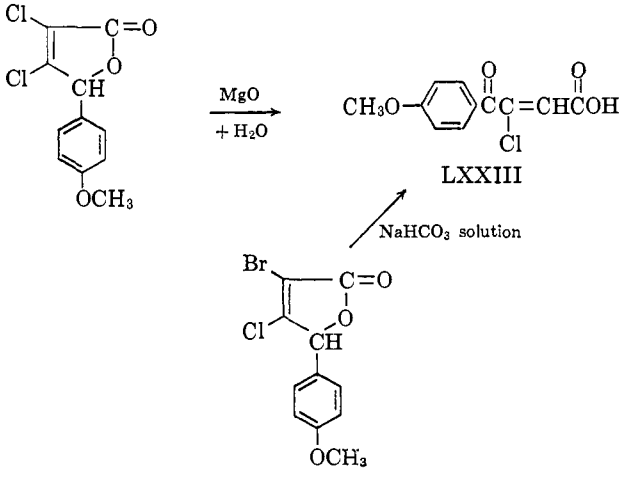
2. With Acid Chlorides

Thionyl chloride and bromide convert α-angelica lactone to halocarboxylic acid halides (17). $\Delta^{\alpha,\beta}$-Butenolide reacted with alcohol in the presence of thionyl chloride to give an ester through the intermediate chloride (65).

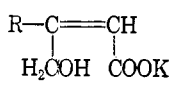


3. Reaction with Bases

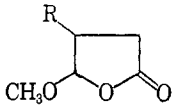
$\Delta^{\beta,\gamma}$-Butenolides are converted to γ-keto acids by heating with sodium hydroxide. α-Arylidene-β-aryl-$\Delta^{\beta,\gamma}$-butenolides give the corresponding α-phenacylcinnamic acid derivatives. Recent work has shown that hydrolysis of $\Delta^{\alpha,\beta}$-butenolides may be accomplished by magnesium oxide in aqueous dioxane, or by sodium bicarbonate solution, to give acrylic acid derivatives (309). With aqueous alkali, the salt of an unsaturated



hydroxycarboxylic acid (LXXIV) is obtained and with alcoholic alkali, an acetal (LXXV) is isolated.



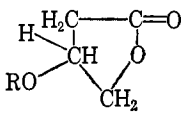
LXXIV



LXXV

B. REACTION WITH ALCOHOLS

When $\Delta^{\alpha,\beta}$-butenolide was heated with an alcohol (ROH, where R = CH_3, C_2H_5, C_3H_7, or C_4H_9) for 16 hr. in a closed vessel, a mixture of products was obtained (65, 66, 270–272). The products were separated by



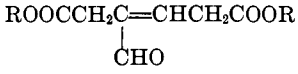
LXXVI

$OHCCH_2CH_2COOR$

LXXVII

$(RO)_2CHCH_2CH_2COOR$

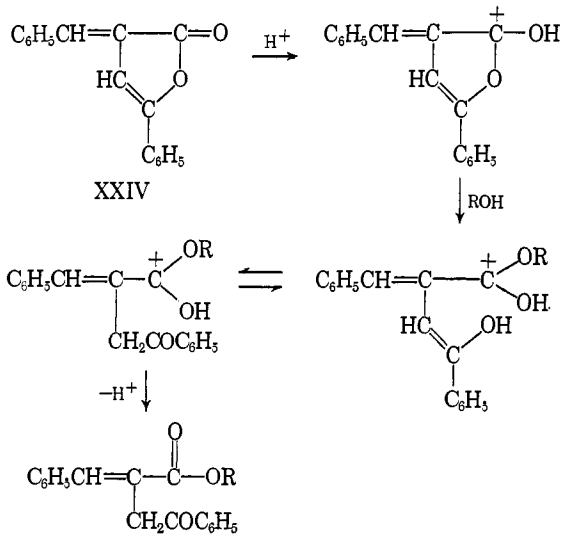
LXXVIII



LXXIX

fractional distillation and identified by preparation of derivatives and infrared and Raman spectra.

α-Angelica lactone reacts with alcoholic hydrogen chloride to give the ethyl ester of levulinic acid (189). The alcoholysis of α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide was studied both in the presence of sodium alkoxide and concentrated sulfuric acid. The alkyl ester of α-phenacylcinnamic acid was obtained. The following mechanism was suggested for the acid-catalyzed alcoholysis of XXIV.

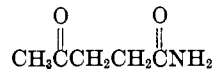


In the presence of diazomethane, α-angelica lactone undergoes transesterification with alcohols (364).

C. REACTION WITH AMMONIA AND AMINES

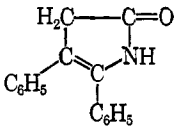
1. With Ammonia and Primary Amines

It was reported in 1885 that α-angelica lactone reacted with ammonia to give levulinic acid amide (LXXX) (366). Later, it was shown that alcoholic



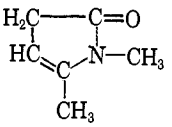
LXXX

ammonia reacted with β,γ-diphenyl-$\Delta^{\beta,\gamma}$-butenolide to give a substituted Δ^2-pyrrolone. With aniline, the N-phenyl analog of LXXXI was obtained (176).



LXXXI

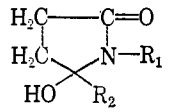
The reaction of α-angelica lactone with aniline, p-toluidine, α-naphthylamine, and β-naphthylamine gave the corresponding amides (210, 211). It was also shown that VIII reacted with methylamine to give 1,2-dimethyl-5-pyrrolinone (LXXXII) (216). Later work has proven conclusively that the anilide of levulinic



LXXXII

acid possesses a straight-chain and not a cyclic structure.

The reaction of $\Delta^{\beta,\gamma}$-butenolides such as α-angelica lactone and γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide with ammonia and primary amines was studied. The products were found to be 2-hydroxypyrrolidone derivatives (LXXXIII). These compounds were synthesized from the corresponding substituted succinic anhydride by reaction with a Grignard reagent (354).

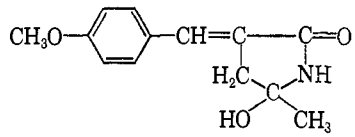


LXXXIII

$R_1 = C_6H_5$; $R_2 = CH_3$
$R_1 = p\text{-}BrC_6H_4$; $R_2 = CH_3$
$R_1 = H$; $R_2 = C_6H_5$
$R_1 = CH_3$; $R_2 = C_6H_5$
$R_1 = C_2H_5$; $R_2 = C_6H_5$
$R_1 = C_3H_7$; $R_2 = C_6H_5$
$R_1 = C_6H_5$; $R_2 = C_6H_5$
$R_1 = p\text{-}BrC_6H_4$; $R_2 = C_6H_5$
$R_1 = H$; $R_2 = p\text{-}CH_3C_6H_4$
$R_1 = H$; $R_2 = p\text{-}CH_3OC_6H_4$

There seems to be a controversy as to whether a cyclic or a straight-chain product is obtained in the

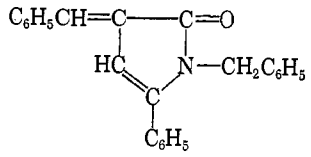
ammonolysis of α-angelica lactone (305). With ammonia, compound VIII gives an amide, which, when treated with anisaldehyde in the presence of diethylamine, gave 3-anisylidene-5-methyl-5-hydroxy-2-pyrrolidone (LXXXIV). The same compound was also ob-



LXXXIV

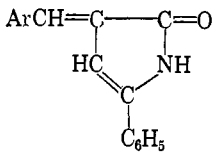
tained when α-anisylidene-γ-methyl-$\Delta^{\beta,\gamma}$-butenolide reacted with alcoholic ammonia. It was concluded that in the crystalline state the cyclic form predominates, and in solution the open-chain form makes the major contribution.

The reaction of α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide with benzylamine gives the benzylamide, which cyclizes with acetic anhydride or hydrochloric acid to a pyrroline derivative (104). More recently, it has

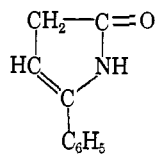


LXXXV

been shown that compounds such as XII react with alcoholic ammonia in the presence of potassium carbonate to give a 2-pyrrolin-5-one (LXXXVI). This reaction is fairly general in that γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide gave 2-phenylpyrrolin-5-one (LXXXVII) (275). These compounds react with Grignard reagents to give



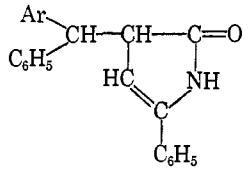
LXXXVI



LXXXVII

Ar = C_6H_5, o-ClC_6H_4, p-ClC_6H_4

2-pyrrolin-5-one derivatives (LXXXVIII), which are also prepared from the corresponding butenolides.



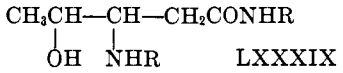
LXXXVIII

Ar = C_6H_5, o-ClC_6H_4, p-ClC_6H_4

From these observations, we may conclude that ammonolysis leads to cyclic products at higher temperature when the reagent is alcoholic ammonia, with or without the presence of a dehydrating agent such as potassium carbonate. With aqueous ammonia at room temperature, only straight-chain amides seem to be formed.

The reaction of α-angelica lactone with benzylamine yields levulinic benzylamide (214). With primary amines, such as ethylamine and propylamine, hydroxypyrrolidones are obtained. These can be dehydrated to pyrrolinones.

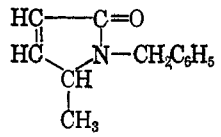
β-Angelica lactone is reported to react with benzylamine and methylamine to give LXXXIX. With



LXXXIX

R = CH_3, $C_6H_5CH_2$

benzylamine at reflux temperatures, the product was 1-benzyl-2-methyl-3-pyrrolin-5-one (XC). The reaction of α,β-dihalo-γ-aryl-$\Delta^{\alpha,\beta}$-butenolides under amino-

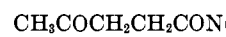


XC

lytic conditions was studied recently, and the products were reported to be β-aroyl-β-haloacrylamides and propionamides (310).

2. *Reaction with Secondary Amines*

α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide reacts with piperidine to give a piperidide. β-Angelica lactone reacts with dimethylamine to give XCI, also obtained from α-angelica lactone and dimethylamine (218).



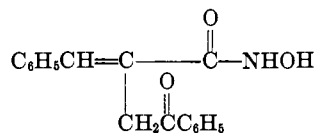
XCI

3. *Tertiary Amines*

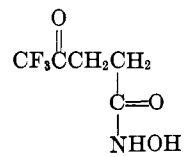
$\Delta^{\beta,\gamma}$-Butenolides are isomerized to the $\Delta^{\alpha,\beta}$ form by tertiary amines. This will be discussed later.

D. REACTION WITH HYDROXYLAMINE AND HYDRAZINE

Butenolides react normally with hydroxylamine and hydrazines to give hydroxamic acids and hydrazides. Thus, α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide and γ-trifluoromethyl-$\Delta^{\beta,\gamma}$-butenolide give compounds XCI and XCII, respectively, with H_2NOH (49, 277).

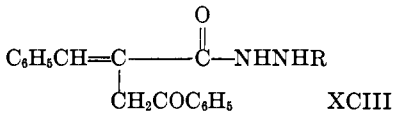


XCI



XCII

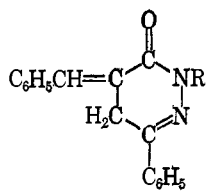
Compound XXIV with hydrazine hydrate forms α-phenacylcinnamic hydrazide (XCIII) and the phenyl-



XCIII

R = H or C_6H_5

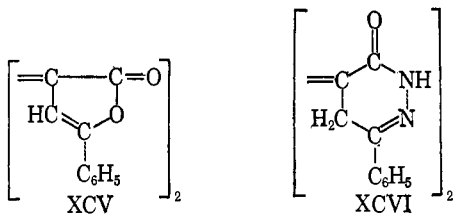
hydrazide with phenylhydrazine. When compound XCIII is heated with aqueous sodium hydroxide or acetic acid–hydrochloric acid, it cyclizes to the pyridazinone derivative, 3-phenyl-5-benzylidene-1,4,5,6-tetrahydropyridazin-6-one (XCIV). These pyridazinones are also obtained when β-aroylpropionic acids are heated with hydrazine sulfate (35, 333) and when α-angelica lactone is heated with N_2H_4 in alcohol (154).



XCIV

R=H or C_6H_5

Similarly, the dilactone XCV gives the dipyridazinone XCVI on reaction with hydrazine hydrate (240).

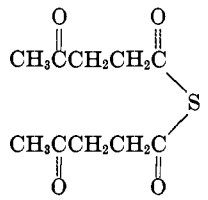


XCV XCVI

E. REACTION WITH THIO COMPOUNDS

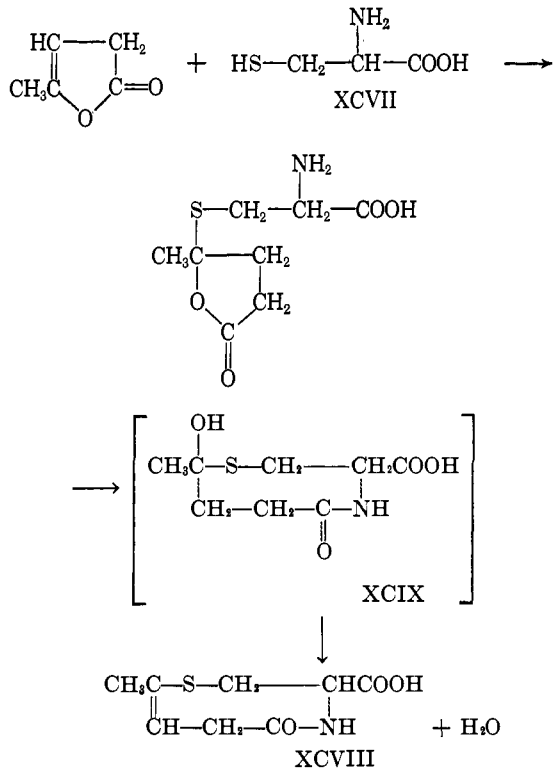
1. Hydrogen Sulfide

α-Angelica lactone and hydrogen sulfide, in the presence of *p*-toluenesulfonic acid, form levulinic thioanhydride (154).



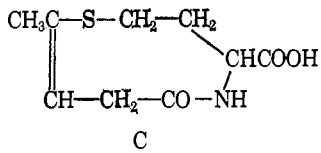
2. Cysteine

The reaction of α- and β-angelica lactones with cysteine (XCVII) in aqueous medium has been investigated (50). Whereas β-angelica lactone gave a water-soluble product, α-angelica lactone formed a crystalline compound which did not contain any free amino, sulfhydryl, or carbonyl groups. The product was represented as a cyclic structure (XCVIII), formed through the intermediacy of XCIX. Homocysteine gave the corresponding nine-membered cyclic

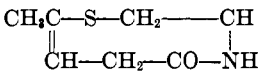


XCVII XCIX XCVIII + H_2O

product C. With β-aminoethanethiol, α-angelica lactone formed a similar product. Among the $\Delta^{\beta,\gamma}$-butenolides studied, the α,α,γ-trimethyl analog reacted with cysteine. α,α,β,γ-Tetramethyl-$\Delta^{\beta,\gamma}$-butenolide and the α,α,β-trimethyl and β,γ-dimethyl analogs failed to react. Among the $\Delta^{\alpha,\beta}$-butenolides, the β,γ-dimethyl compound did not react with cysteine. This demonstrates that a β-substituent on the butenolide ring prevents reaction with cysteine, while substitution at α- and γ-positions does not inhibit the reaction. These reactions constituted part of a study to determine whether the antibiotic activity of certain unsaturated lactones was associated with their ability to react with the sulfhydryl and amino groups of enzyme proteins. No correlation could, however, be made.



C

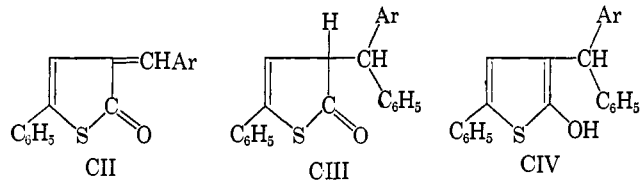


CI

3. Reaction of α-Arylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides with Thioacetic Acid

Thioacetic acid has been shown to react with α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (XXIV) and α-*o*-chlorobenzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide in the presence of pyridine to give the corresponding 2-phenyl-

4-arylidene-5-oxo-Δ^2-thiolene derivative (CII). Compounds of this type may be considered as thiolactones and they exhibit behavior consistent with their lactone character. Thus, they react with benzene under Friedel–Crafts conditions or with phenylmagnesium bromide to give products CIII and CIV, formed by 1,4-addition to the α,β-unsaturated carbonyl moiety. Compounds CIII and CIV exist in tautomeric forms. They show hydroxyl absorption in the infrared spectrum (278).



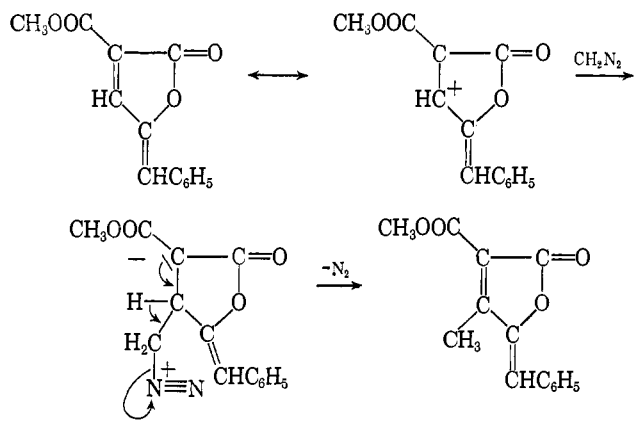
CII CIII CIV

Ar = C_6H_5, $o-ClC_6H_4$

F. WITH DIAZOMETHANE

It has been observed that α-angelica lactone reacts with diazomethane at 0° in the presence of alcohols to yield alkyl levulinates (364).

If a hydroxyl or carboxyl group is present in the butenolide nucleus, the methoxy ether or methyl ester is obtained (3, 254, 323). α-Carbomethoxy-γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolide reacts with diazomethane to give the β-methyl derivative as shown below.



Thus, C-methylation occurs rather than formation of cyclopropane derivatives. Similarly, α-cyano-β-methyl-γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolide was prepared (3).

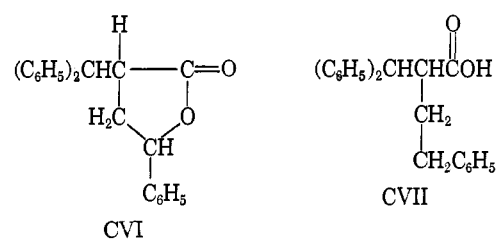
G. REDUCTIONS

A systematic study of the catalytic hydrogenation of isomeric butenolides indicated that $\Delta^{\beta,\gamma}$ butenolides usually give desoxy acids while the $\Delta^{\alpha,\beta}$-isomers form valerolactone derivatives (159, 160). However, $\Delta^{\beta,\gamma}$-butenolides containing a β-substituent give mixtures of desoxy acids and valerolactone derivatives (Table V). α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide is reduced by zinc and acetic acid or alcoholic sulfuric acid to α-benzyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (336). When the exocyclic double bond is absent, saturation of the lactone ring proceeds normally. Thus, α-benzhydryl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (CV) gave α-benzhydryl-γ-phenyl-γ-butyrolactone (CVI) when reduced with hydrogen on palladium–charcoal (109) but was reduced to 4-phenyl-2-benzhydrylbutyric acid (CVII) in alcohol medium.

TABLE V

PRODUCTS OF REDUCTION OF BUTENOLIDES

Butenolide	Desoxy acid	Lactone
α-Angelica lactone	Valeric acid	
β-Angelica lactone		Valerolactone
α,α,γ-Trimethyl-$\Delta^{\beta,\gamma}$-butenolide	α,α-Dimethylvaleric acid	
α,γ,γ-Trimethyl-$\Delta^{\alpha,\beta}$-butenolide		γ-Methyl-γ-valerolactone
α,α,β-Trimethyl-$\Delta^{\beta,\gamma}$-angelica lactone	α,α,β-Trimethylvaleric acid	α,α,β-Trimethylvalerolactone
β-Methyl-$\Delta^{\beta,\gamma}$-angelica lactone	γ-Methylvaleric acid	β-Methyl-γ-valerolactone
α,α,β-Trimethyl-$\Delta^{\beta,\gamma}$-butenolide	α,α,β-Trimethylbutyric acid	α,α,β-Trimethylbutyrolactone
α,α-Dimethyl-β-phenyl-$\Delta^{\beta,\gamma}$-butenolide	α,α-Dimethyl-β-cyclohexylbutyric acid (complete reduction)	α,α-Dimethyl-β-cyclohexylbutyric acid
	α,α-Dimethyl-β-phenylbutyric acid (incomplete reduction)	α,α-Dimethyl-β-phenylbutyrolactone
α-Anisylidene-γ-methyl-$\Delta^{\beta,\gamma}$-butenolide	α-Anisylvaleric acid	α-Anisyl-γ-valerolactone



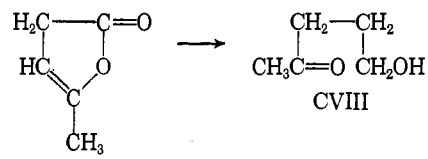
CVI CVII

H. REACTION WITH COMPLEX METAL HYDRIDES

Much work has been done on the reaction of butenolides with complex metal hydrides (110, 123, 147, 273, 274). The reduction of butenolides by lithium aluminum hydride (LAH) proceeds in a manner consistent with its action on lactones in general; that is, hydrogenolysis of the carbonyl oxygen bond occurs to form alcohol and aldehyde functions. A stable keto form (which may be further reduced to an alcohol function) is obtained, if the initial product is an enol rather than an alcohol.

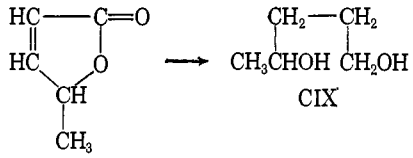
1. Reaction of LAH with α- and β-Angelica Lactones

α-Angelica lactone reacts with LAH in N-ethylmorpholine at 90° to give a 65% yield of 3-acetylpropanol (CVIII). Under similar conditions, β-angelica lactone



CVIII

gives a 10% yield of 1,4-pentanediol (CIX), isolated as the diacetate. Since γ-valerolactone also gives the

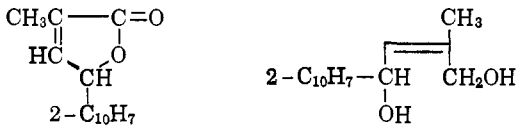


CIX

diol CIX (123), it is possible that γ-valerolactone is an intermediate in the reduction of β-angelica lactone.

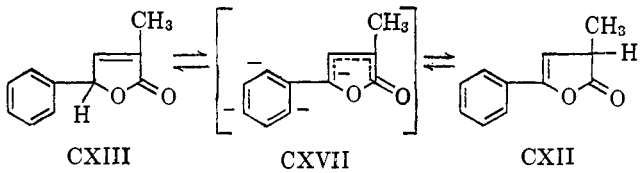
2. Reaction of LAH with Other Isomeric Butenolides

The formation of diols seems to characterize the reduction of $\Delta^{\alpha,\beta}$-butenolides by LAH. Thus, γ-(2-naphthyl)-α-methyl-$\Delta^{\alpha,\beta}$-butenolide (CX) forms 2-methyl-4-(2-naphthyl)-2-butene-1,4-diol (CXI) in 30% yield at room temperature (273).

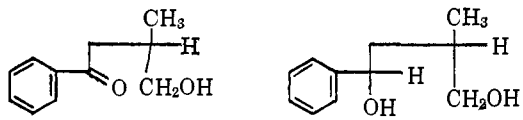


CX CXI

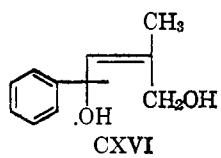
A systematic quantitative study of the reduction of a pair of isomers, α-methyl-γ-phenyl-$\Delta^{\beta,\gamma}$- and -$\Delta^{\alpha,\beta}$-butenolides (CXII, CXIII), has been carried out. Variations in the LAH–butenolide mole ratio and in reaction times were examined (273, 274, 285). CXII gave the keto alcohol, β-(hydroxymethyl)butyrophenone (CXIV), and the saturated diol, 2-methyl-4-phenyl-1,4-butanediol (CXV), whereas CXIII formed the keto alcohol CXIV, unsaturated diol, *cis*-2-methyl-4-phenyl-2-butene-1,4-diol (CXVI), and the saturated diol. The formation of the same keto alcohol and saturated alcohol from both isomers indicates the intermediacy of a common hybrid anion (CXVII) during the course of reduction. The results showed that the



CXIII CXVII CXII



CXIV CXV

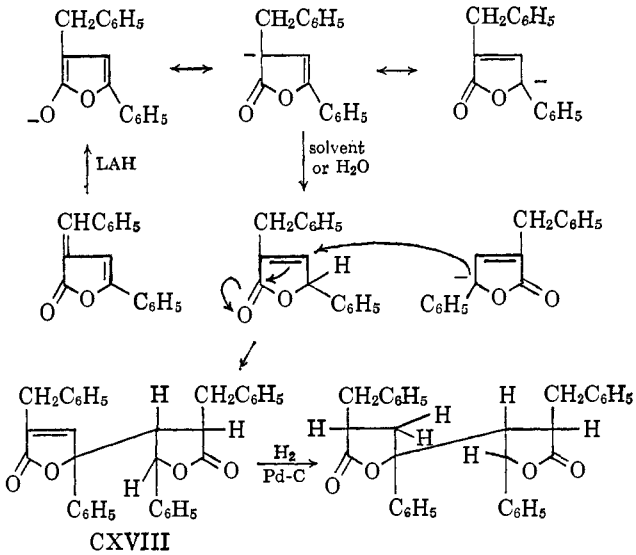


CXVI

variation of the LAH–butenolide ratio leads to formation of a variety of complexes, which yield the same products on hydrolysis. Experiments with different mole ratios indicated that the $\Delta^{\beta,\gamma}$-butenolide yielded mainly the keto alcohol CXIV with the unchanged material recovered as the $\Delta^{\alpha,\beta}$ isomer. The $\Delta^{\alpha,\beta}$ isomer gave the keto alcohol CXIV as the principal product.

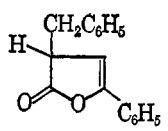
3. Reduction of α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide

Earlier work on the reduction of XXIV indicated that the principal product was α-benzyl-γ-phenyl-$\Delta^{\alpha,\beta}$-butenolide, when the reaction was conducted in refluxing ether or tetrahydrofuran with a 2-mole excess of LAH (225). Further studies (110) revealed, however, that the product was dimeric. The suggested mechanism for this interesting transformation is shown below.



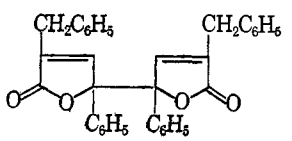
CXVIII

The structure of CXVIII was established by analytical data, hydrolysis, and aminolysis studies and by spectral evidence (infrared, ultraviolet, and proton magnetic resonance). Such a structure would account for the hydrolysis of CXVIII to β-benzoyl-α-benzylpropionic acid (CXIX). The formation of CXIX was explained by the intermediacy of CXX. Similar dimers were also obtained from the *o*-chloro-, *p*-chloro-, *o*-methoxy-, and *p*-methoxybenzylidene analogs of XXIV.



CXX

When the reduction of XXIV was carried out with LAH at −25°, a 20% yield of bislactone CXXI was obtained. This was also prepared by the cyclization of β-benzyl-α-benzylpropionic acid (CXIX) with acetic anhydride.



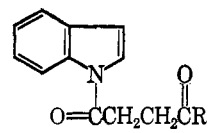
CXXI

Sodium borohydride reduction of XXIV led to the formation of high melting, high molecular weight compound, which was not characterized.

I. REACTION WITH ORGANOMETALLIC REAGENTS

1. Reaction of $\Delta^{\beta,\gamma}$-Butenolides with Grignard Reagents

γ-Phenyl-$\Delta^{\beta,\gamma}$-butenolide and α-angelica lactone (VIII) have been reported to act as acylating agents toward indolylmagnesium iodide to give 1-β-benzoylpropionylindole (CXXIIa) and 1-levulinoylindole (CXXIIb), respectively (174).



CXXIIa, R = C_6H_5
b, R = CH_3

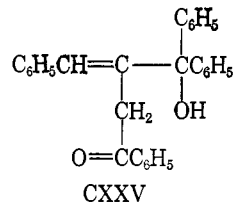
2. Reaction of Grignard Reagents with $\Delta^{\beta,\gamma}$-Butenolides with an Exocyclic Bond in the α-Position

Recent work (276) on vinylogous acid halides, such as α-chloromethylene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide, with Grignard reagents has shown that α-arylidenebutenolides are obtained in high yields, as mentioned earlier.

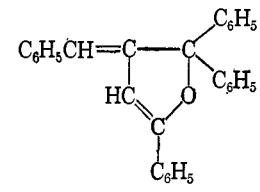
With excess phenylmagnesium bromide, α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (XXIV) is reported (109) to give α-benzhydryl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (CXXIII), formed by the 1,4-addition of the reagent to the α,β-unsaturated carbonyl moiety. A small quantity of α-benzhydryl-γ-phenyl-$\Delta^{\alpha,\beta}$-butenolide (CXXIV) is also obtained. (The reaction probably proceeds *via* a resonance-stabilized allylic carbanion, similar to that proposed for the LAH reduction of XXIV.) Compound CXXIII is converted to CXXIV by acetic anhydride, triethylamine, heat, or even benzylamine (a reagent which usually forms benzylamides with γ-lactones). The structure of CXXIII was established by analytical data, reduction with hydrogen on palladium–charcoal to α-benzhydryl-γ-phenyl-γ-butyrolactone (CVI), and alkaline hydrolysis to 2-phenacyl-3,3-diphenylpropionic acid. The infrared spectrum of CXXIII, however, showed a strong carbonyl absorption at 1783 cm.$^{-1}$, which is rather low for $\Delta^{\beta,\gamma}$-butenolides having no exocyclic double bond at the α-position, while CXXIV exhibited the carbonyl band at 1750 cm.$^{-1}$ characteristic for $\Delta^{\alpha,\beta}$-butenolides. Analogs of CXXIII and CXXIV were obtained starting with α-(*p*-chlorobenzylidene)-, α-(*o*-chlorobenzylidene)-, and α-(*p*-anisylidene)butenolides. The suggestion has been made that the so-called $\Delta^{\alpha,\beta}$ isomers obtained in these Grignard reactions might be bislactones of the type CXXI (256). For one thing, the melting points of these compounds are much higher than expected for the $\Delta^{\alpha,\beta}$ compounds but are in the range usually found for such bislactones. Pending further investigation and a satisfactory method for determination of molecular weights of bislactones, this assignment of structure CXXIV remains in doubt.

3. Reaction of α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide with Phenyllithium

Compound XXIV reacts with phenyllithium to give the product of 1,2-addition, 1,1-diphenyl-2-phenacylcinnamyl alcohol (CXXV), which is unstable and is cyclized by heating with acetic anhydride to 2,2,5-triphenyl-3-benzylidene-2,3-dihydrofuran (CXXVI).



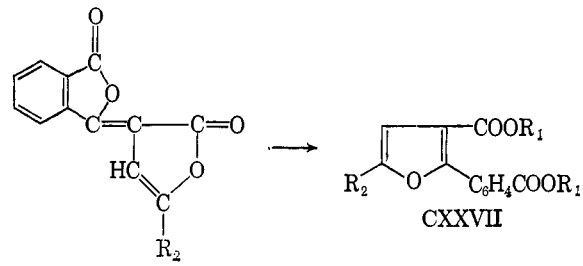
CXXV



CXXVI

J. CONVERSION TO FURAN DERIVATIVES

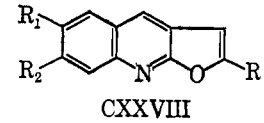
Butenolides may be regarded as dihydro-2(3H)- or -2(5H)-furanones and might be expected to be converted easily to furan derivatives. It has been pointed out in the last section that α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (XXIV) forms a substituted dihydrofuran (CXXVI) on reaction with phenyllithium, followed by dehydrative cyclization. Butenolides derived from phthalic anhydride and γ-keto acids are converted to furan carboxylate derivatives (CXXVII)



CXXVII

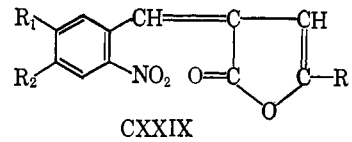
a, R_1 = CH_3; R_2 = *p*-$CH_3C_6H_4$
b, R_1 = C_2H_5; R_2 = *p*-$CH_3C_6H_4$
c, R_1 = H; R_2 = *p*-$CH_3C_6H_4$
d, R_1 = CH_3; R_2 = C_6H_5
e, R_1 = H; R_2 = C_6H_5
f, R_1 = H; R_2 = CH_3
g, R_1 = CH_3; R_2 = *p*-$CH_3OC_6H_4CH{=}CH$ (*p*-methoxystyryl)
h, R_1 = H; R_2 = *p*-$CH_3OC_6H_4CH{=}CH$

on treatment with a 10:1 mixture of methanol–sulfuric acid for 32 hr. (31). Another interesting class of furan derivatives, furanoquinolines (CXXVIII), has been prepared by the reduction of *o*-nitrobenzylidenebuteno-



CXXVIII

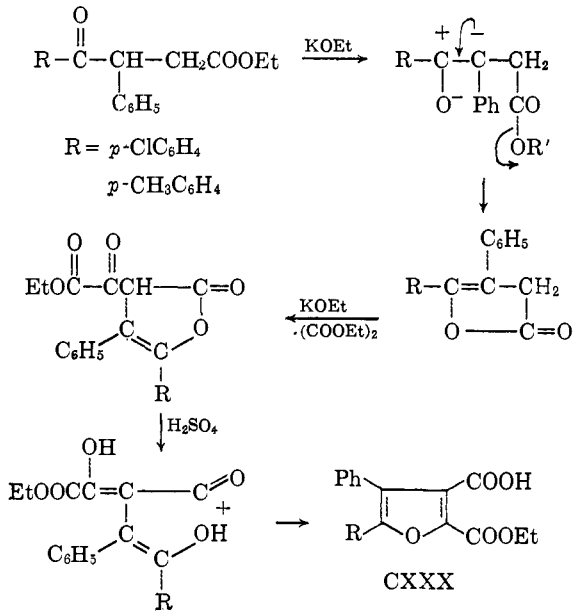
R = 3,4-$(CH_3O)_2C_6H_3$; R_1 = R_2 = CH_3O
R_1 = R_2 = H
R_1, R_2 = (—O—CH_2—O—)



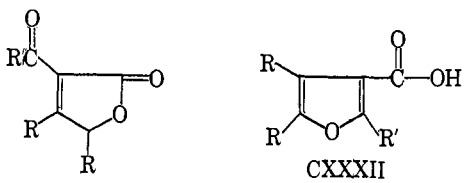
CXXIX

R = 3,4-$(CH_3O)_2C_6H_3$; $R_1 = R_2 = CH_3O$
$R_1 = R_2 = H$
R_1, R_2 = methylenedioxy (—O—CH_2—O—)

lides (CXXIX) with zinc and acetic acid. Recently, the conversion of butenolides to furancarboxylic acids has been reported (16).



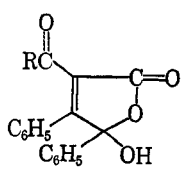
An interesting rearrangement involves the conversion of α-acyl-$\Delta^{\alpha,\beta}$-butenolides (3-acyl-2,5-dihydro-2-furanones) (CXXXI) to furan-3-carboxylic acids (CXXXII) on heating with an acetic acid–hydrochloric acid mixture (195–199). A number of furancarboxylic acids have been prepared in this manner. Aged samples of α-acetyl-β,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide and its α-benzoyl



CXXXI CXXXII

R = n-C_3H_7; R′ = CH_3
R = C_2H_5; R′ = CH_3
R = R′ = CH_3
R = $C_{11}H_{23}$; R′ = CH_3
R = C_6H_5; R′ = CH_3
R = R′ = C_6H_5

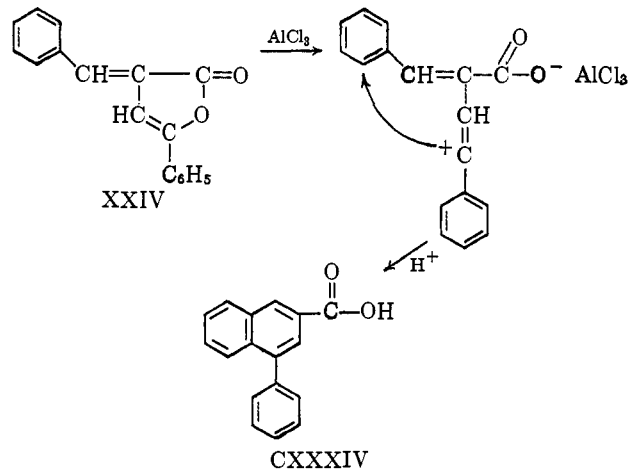
analog, however, gave the corresponding α-acyl-β,γ-diphenyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide (CXXXIII).



CXXXIII

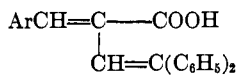
K. CONVERSION TO NAPHTHALENE DERIVATIVES

The behavior of α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (XXIV) in the presence of anhydrous aluminum chloride was studied (106). The product obtained was shown to be 4-phenyl-2-naphthoic acid (CXXXIV), formed by intramolecular alkylation. The reaction presumably proceeds *via* electrophilic attack at the *ortho* position of the arylidene ring by a resonance stabilized carbonium ion, generated by alkyl–oxygen bond cleavage, with the assistance of aluminum chlo-



XXIV CXXXIV

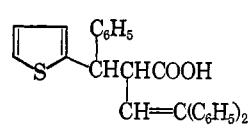
ride. The driving force for the cyclization is the stabilization afforded by the newly formed aromatic system. This reaction is rather complex and products other than naphthoic acids are formed, depending primarily on the nature of arylidene moiety and, to a lesser extent, on the medium (105). The butenolides obtained from α-naphthaldehyde and *o*- and *p*-chlorobenzaldehyde also gave naphthoic acids, but with those prepared from *p*-anisaldehyde, *o*-methoxybenzaldehyde, furfural, and 2-thenaldehyde, intermolecular alkylation occurred with the solvent (benzene) participation to give 1,1-diphenyl-4-aryl-1,3-butadiene-3-carboxylic acids (CXXXV). α-2-Thienylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide reacted with benzene to give a butadiene carboxylic



CXXXV

Ar = *o*-$CH_3OC_6H_4$, *p*-$CH_3OC_6H_4$, 2-furyl, 2-thienyl

acid, but this reacted further with an additional mole of benzene to give the 1,4- addition product CXXXVI.

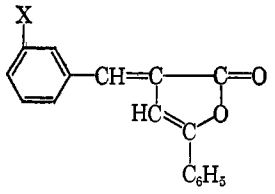


CXXXVI

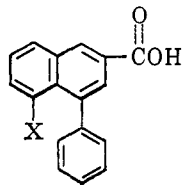
A systematic study on the variations in catalyst, temperature, and solvents revealed that neither stannic chloride nor boron trifluoride etherate was effective and anhydrous aluminum chloride was the best catalyst.

Benzene was the preferred solvent, although reaction did take place in other solvents such as toluene, dichloromethane, and tetrachloroethane.

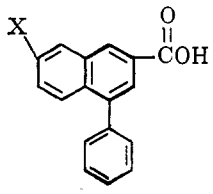
Very recently it has been found (107) that butenolides obtained from *meta*-substituted benzaldehydes give a mixture of two isomeric phenylnaphthoic acids, 4-phenyl-5-X-2-naphthoic acid (CXXXVII) and 4-phenyl-7-X-2-naphthoic acid (CXXXVIII).



X=Cl,Br

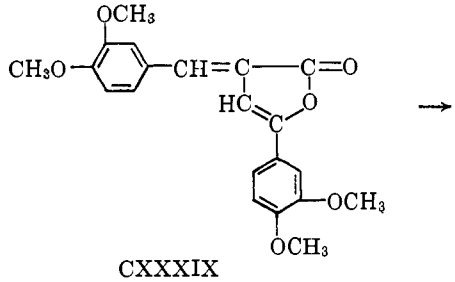


CXXXVII

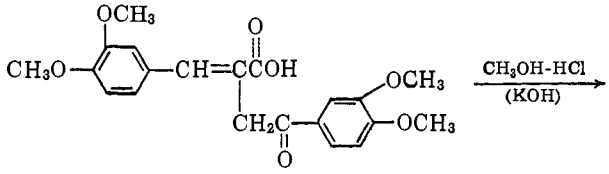


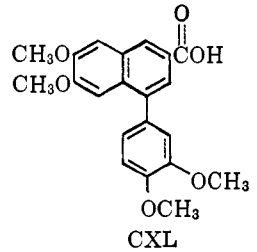
CXXXVIII

Several other methods are available for the conversion of lactones to naphthoic acids. Thus, α-veratrylidene-γ-veratryl-$\Delta^{\beta,\gamma}$-butenolide (CXXXIX) gives 6,7-dimethoxy-4-veratryl-2-naphthoic acid (CXL) on heating with methanolic hydrogen chloride.



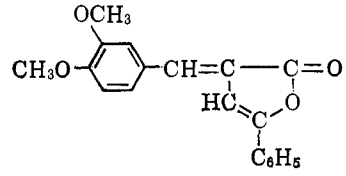
CXXXIX



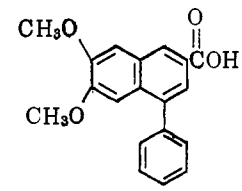


CXL

Another method involves treating a chloroform solution of butenolide CXLI with iodine. 6,7-Dimethoxy-4-phenyl-2-naphthoic acid (CXLII) is prepared in this manner.

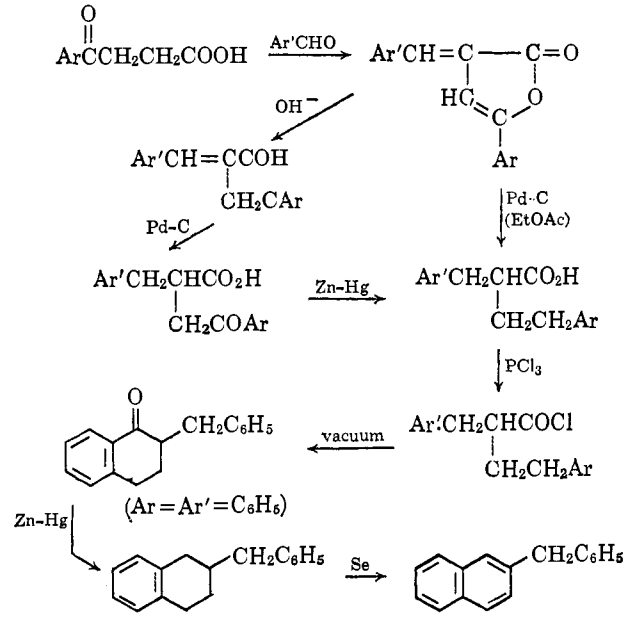


CXLI



CXLII

A more circuitous route involves the following steps.



2-benzyl-naphthalene

The following naphthalene derivatives were prepared in similar fashion: 2-benzyl-7-methoxynaphthalene, 2-*p*-methoxybenzyl-7-methoxynaphthalene, and 2-benzyl-6,7-dimethoxynaphthalene.

The most facile conversion of butenolides to naphthalene derivatives involves heating the lactones under reflux with a mixture of glacial acetic acid and concentrated hydrochloric acid for periods ranging from 20 min. to 6 hr. (70, 71). This method has been effectively used for the isomerization of butenolides with methoxy or methylenedioxy substituents on the α-arylidene and (or) on the γ-aryl nuclei. A variety of naphthoic acids, esters, and arenes (obtained by the decarboxylation of the acids with copper bronze in quinoline) were prepared (Table VI). The advantage of this method seems to be the purity of the products. The following mechanism has been suggested for the isomerization.

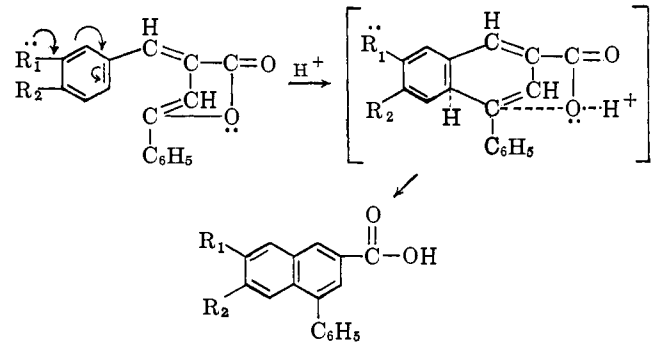
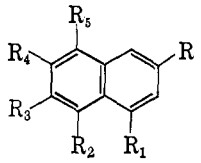


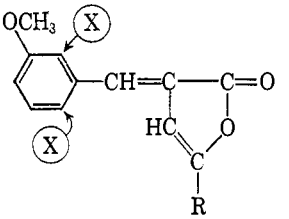
TABLE VI

NAPHTHALENE DERIVATIVES



R	R_1	R_2	R_3	R_4	R_5	Ref.
$C_6H_5CH_2$	H	H	H	H	H	33
$C_6H_5CH_2$	H	H	H	CH_3O	H	33
p-$CH_3OC_6H_4CH_2$	H	H	F	CH_3O	H	33
$C_6H_5CH_2$	H	H	CH_3O	CH_3O	H	33
COOH	p-$CH_3OC_6H_4$	H	H	H	H	70
COOH	3,4-$(CH_3O)_2C_6H_3$	H	–O–CH_2–O–		H	70
COOH	3,4-$(CH_3O)_2C_6H_3$	H	H	CH_3O	H	70
COOH	C_6H_5	H	H	CH_3O	H	70
COOH	p-ClC_6H_4	H	H	CH_3O	H	70
COOH	p-$CH_3C_6H_4$	H	H	CH_3O	H	70
COOH	o-$CH_3OC_6H_4$	H	H	CH_3O	H	70
COOH	p-ClC_6H_4	H	–O–CH_2–O–		H	70
COOH	C_6H_5	H	–O–CH_2–O–		H	70
$COOCH_3$	p-$CH_3OC_6H_4$	H	H	H	H	70
$COOCH_3$	3,4-$(CH_3O)_2C_6H_3$	H	–O–CH_2–O–		H	70
$COOCH_3$	3,4-$(CH_3O)_2C_6H_3$	H	H	CH_3O	H	70
$COOCH_3$	C_6H_5	H	H	CH_3O	H	70
$COOCH_3$	p-ClC_6H_4	H	H	CH_3O	H	70
$COOCH_3$	p-$CH_3C_6H_4$	H	H	CH_3O	H	70
$COOCH_3$	o-$CH_3OC_6H_4$	H	H	CH_3O	H	70
$COOCH_3$	p-ClC_6H_4	H	–O–CH_2–O–		H	70
$COOCH_3$	C_6H_5	H	–O–CH_2–O–		H	70
COOH	p-$CH_3OC_6H_4$	H	–O–CH_2–O–		H	71
COOH	p-ClC_6H_4	H	CH_3O	CH_3O	H	71
COOH	C_6H_5	H	CH_3O	CH_3O	H	71
COOH	p-$CH_3C_6H_4$	H	–O–CH_2–O–		H	71
COOH	p-$CH_3OC_6H_4$	H	CH_3O	CH_3O	H	71
COOH	p-$CH_3OC_6H_4$	H	CH_3O	H	H	71
COOH	C_6H_5	H	CH_3O	H	H	71
COOH	p-$CH_3OC_6H_4$	H	H	H	H	71
COOH	C_6H_5	H	H	H	H	71, 106
$COOCH_3$	p-$CH_3OC_6H_4$	H	–O–CH_2–O–		H	71
$COOCH_3$	p-ClC_6H_4	H	CH_3O	CH_3O	H	71
$COOCH_3$	C_6H_5	H	CH_3O	CH_3O	H	71
$COOCH_3$	p-$CH_3C_6H_4$	H	–O–CH_2–O–		H	71
$COOCH_3$	p-$CH_3OC_6H_4$	H	CH_3O	CH_3O	H	71
$COOCH_3$	p-$CH_3OC_6H_4$	H	CH_3O	H	H	71
H	C_6H_5	H	H	H	CH_3O	70
H	3,4-$(CH_3O)_2C_6H_3$	H	–O–CH_2–O–		H	70
H	p-ClC_6H_4	H	H	CH_3O	H	70
H	p-ClC_6H_4	H	–O–CH_3–O–		H	70
H	C_6H_5	H	–O–CH_2–O–		H	70
H	C_6H_5	H	H	H	H	105, 202
COOH	C_6H_5	H	H	H	Cl	105, 202
H	C_6H_5	H	H	H	Cl	105, 202
COOH	C_6H_5	H	Cl	H	H	105, 202
H	C_6H_5	H	Cl	H	H	105, 202
COOH	C_6H_5	H	H	Cl	H	105, 202
COOH	C_6H_5	Cl	H	H	H	107, 277
H	C_6H_5	H	H	Cl	H	107, 277
H	C_6H_5	Cl	H	H	H	107, 277
COOH	C_6H_5	H	H	Br	H	107, 277
COOH	C_6H_5	Br	H	H	H	107, 277
H	C_6H_5	H	H	Br	H	107, 277
H	C_6H_5	Br	H	H	H	107, 277

Some butenolides, *e.g.*, those derived from *m*-nitrobenzaldehyde and benzaldehyde, failed to react under these conditions. Even aluminum chloride in nitrobenzene (at 25 and 100°), sodium chloride melt, or iodine in chloroform, did not bring about the conversion. From these experiments it is evident that the substituents on both the arylidene and the aryl moieties determine whether isomerization will occur. It is surprising, however, that *m*-methoxy-substituted benzylidenebutenolides (CXLIII) gave 6-methoxy-4-aryl-2-naphthoic acids exclusively, since a mixture of 6- and 8-methoxynaphthalene derivatives would be expected.

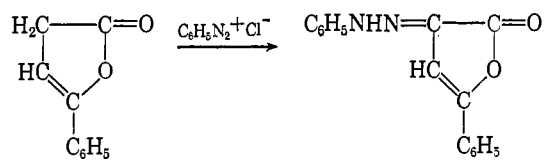


CXLIII

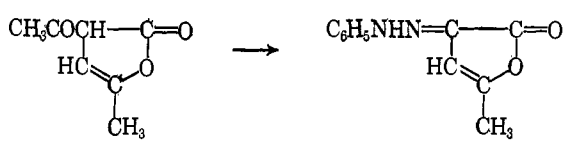
R = C_6H_5, *p*-ClC_6H_4, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *o*-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$

L. REACTION WITH ARYLDIAZONIUM CHLORIDE

γ-Phenyl-$\Delta^{\beta,\gamma}$-butenolide reacts with benzenediazonium chloride to give the α-phenylazo analog CXLIV (64). γ-Methyl-α-phenylazo-$\Delta^{\alpha,\beta}$-butenolide (CXLVI) was obtained from CXLV (171).

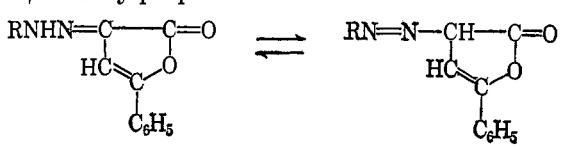


CXLIV



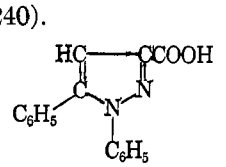
CXLV CXLVI

Compounds of type CXLIV have been prepared from β-benzoylpropionic acid.



R = C_6H_5, = *p*-$CH_3C_6H_4$, = *m*-ClC_6H_4, = *p*-ClC_6H_4

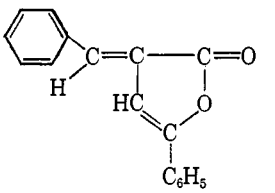
Compound CXLIV, when treated with alcoholic alkali or acid, gave 1,5-diphenylpyrazole-3-carboxylic acid (CXLVII) (240).



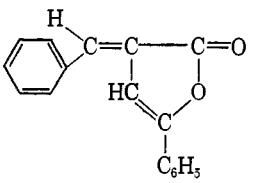
CXLVII

M. GEOMETRIC ISOMERS OF α-BENZYLIDENE-γ-PHENYL-$\Delta^{\beta,\gamma}$-BUTENOLIDE

The exocyclic double bond of α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide permits the existence of two geometric configurations (XXIV and XXIVa). Both isomers have been described; however, their relative configurations have not been established.

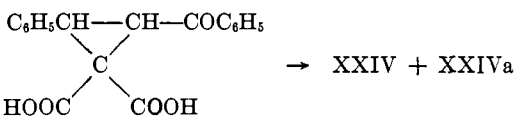


XXIV



XXIVa

The isomers were prepared in the following manner. α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (m.p. 156°), obtained from β-benzoylpropionic acid and benzaldehyde, was hydrolyzed with alcoholic potassium hydroxide to α-phenacylcinnamic acid. This compound was crystallized from benzene, and an isomeric α-phenacylcinnamic acid was isolated from the mother liquor. This compound gave the isomeric butenolide, m.p. 167°, when heated with acetic anhydride and sulfuric acid. A second method of preparation of this isomer consists of heating 2-phenyl-3-benzoylcyclopropanedicarboxylic acid to 150° and extracting the residue with ether. The extract gives the two isomers of XXIV.



N. DIMERIZATION OF BUTENOLIDES

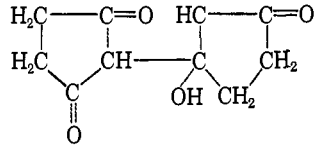
The dimerizations during hydride reduction of α-arylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides have been discussed earlier.

1. Dimerization of α- and β-Angelica Lactones

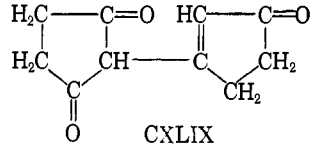
Either α- or β-angelica lactone or a mixture form dimers at 20–200° in the presence of catalysts such as tertiary amines, alkali metal alkoxides, alkali metal hydroxides, and free alkali metals (367). Of the two, β-angelica lactone was more reactive than the α-form. A mixture of two dimers with a molecular formula of $C_{10}H_{12}O_4$ was obtained. The dimers were hydrogenated to saturated dilactones of the formula $C_{10}H_{14}O_4$. On alkaline hydrolysis, they yielded acids of undetermined structures.

The same dimers were also obtained when sodium methoxide and sodium metal were used as catalysts (368). The reaction of β-angelica lactone with freshly

prepared sodium methoxide in a nitrogen atmosphere (92, 95) gave three products—a water-soluble material melting at 151° and a compound melting at 88–92°; product CXLIX was also obtained from CXLVIII by alkaline hydrolysis followed by acidification. The possibility of rearrangement of β-angelica lactone into



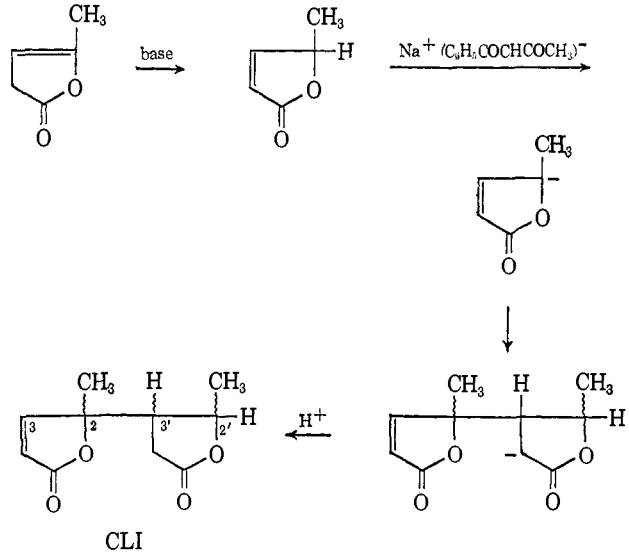
CXLVIII



CXLIX

1,3-cyclopentadione was considered. It may be pointed out that α-phenyl-γ-benzyl-$\Delta^{\alpha,\beta}$-butenolide gave 1,3-diphenyl-2,5-dioxocyclopentane (CL) when treated with sodium metal in methanol and also the dimer of CL (91).

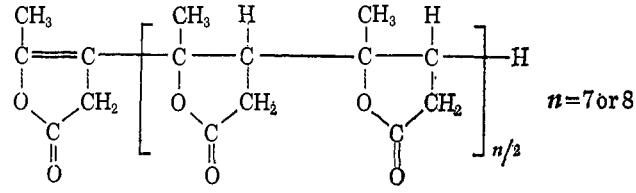
α-Angelica lactone dimerizes in the presence of anhydrous potassium carbonate to give 5,5′-dioxo-2,2′-dimethyl-2,2′,3′,4′,5,5′-hexahydro-2,3′-bifuran (217) (CLI). Recently, it has been reported that in the presence of the sodium salt of benzoylacetone, β-angelica lactone undergoes Michael addition with the active methylene group to give the dimer CLI (329, 330). Since α-angelica lactone gave the same dimer, it was suggested that α-lactone isomerized in presence of base to the β-form, which then dimerized. The following mechanism was suggested.



CLI

2. Polymerization of Butenolides

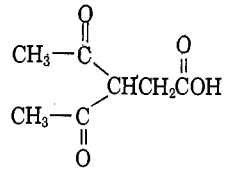
$\Delta^{\alpha,\beta}$-Butenolide was found to be a poor monomer (170, 258). α-Angelica lactone gave a dark red polymer (CLII) when heated with boron trifluoride in carbon disulfide (228, 296) by a stepwise polymerization, rather than a chain mechanism usually encountered in vinyl polymerizations. With liquid ammonia, the polymer gave a polylactam. The polymer possessed a head to tail structure and was represented as



CLII

No isomerization to the β-angelica lactone occurred. α-Angelica lactone formed copolymers with acrylonitrile (155).

When α-angelica lactone was kept at −20° with acetic anhydride and boron trifluoride, however, it gave a complex, $C_7H_8O_4 \cdot BF_3$ (94). This reacted with saturated aqueous cupric acetate to give a green salt and a blue copper salt, $C_7H_8O_4Cu \cdot 2H_2O$. When this was treated with sodium carbonate and then dilute sulfuric acid, β,β-diacetylpropionic acid (CLIII) was obtained.

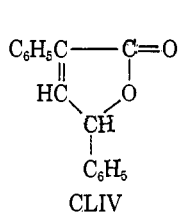


CLIII

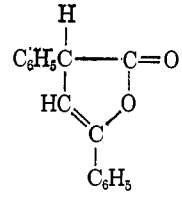
The oxidative dimerization of γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides leads to the formation of Pechmann dyes (IV), already reviewed (177) elsewhere.

O. BISLACTONES

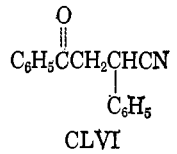
Considerable confusion exists about the structure of products obtained by the action of acetic anhydride or acetyl chloride on α-aryl-β-aroylpropionic acids. Thus, α-phenyl-β-benzoylpropionic acid gave two isomers melting at 109 and 284°. They were formulated as the $\Delta^{\beta,\gamma}$ and $\Delta^{\alpha,\beta}$ isomers, respectively (9, 133). It was claimed that the higher melting form was obtained in high yield by sulfuric acid hydrolysis of α-phenyl-β-benzoylpropionitrile (133) (CLVI). It was shown recently (278) that this compound, m.p. 284°, was a



CLIV

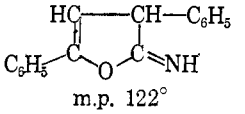


CLV

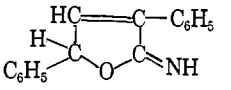


CLVI

Δ^3-pyrrolin-5-one derivative (CLIX). Two such compounds were called "iminocrotonolactones" (281) and were formulated as CLVII and CLVIII. The higher melting compound was prepared from CLVI by acid hydrolysis or by the acid-catalyzed cyclization of α-phenyl-β-benzoylpropionamide (278, 281). The same

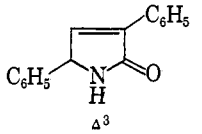


m.p. 122°
CLVII

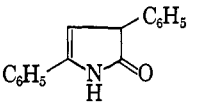


m.p. 284°
CLVIII

compound was also obtained by the cyclodehydration of α-phenyl-β-benzylpropionic acid in the presence of ammonium acetate (103). It was formulated as the Δ^2 isomer (CLX) rather than the Δ^3 isomer (CLIX).



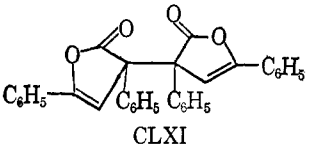
Δ^3
CLIX



Δ^2
CLX

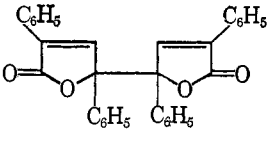
A saturated Δ^2 compound of the type CLX should show carbonyl absorption at 1705 cm.$^{-1}$ (275), while CLIX exhibits a band at 1685 cm.$^{-1}$. Compound CLIX was also obtained when α,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide (m.p. 109°) was treated with ammonia and potassium carbonate (278).

Of the two isomers obtained from α-phenyl-β-benzoylpropionic acid, the lower melting form has been shown to be the $\Delta^{\alpha,\beta}$ isomer (182, 281, 355, 360, 369). The higher melting form, which is still considered by some investigators as the $\Delta^{\beta,\gamma}$ isomer (15, 63), has been formulated as a bislactone (CLXI) (268). A similar compound was prepared by the photodecomposition of α-diazoacetophenone (363) by itself and in benzonitrile (152). Recent work on the thermal decomposition of α-diazoacetophenone and on bislactones (369)



CLXI

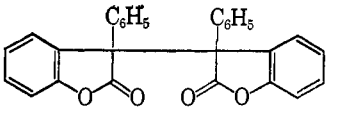
has proved conclusively that the 284° melting material is the $\Delta^{\alpha,\beta}$-bislactone. The bislactone obtained from α-benzyl-β-benzoylpropionic acid (110) has already



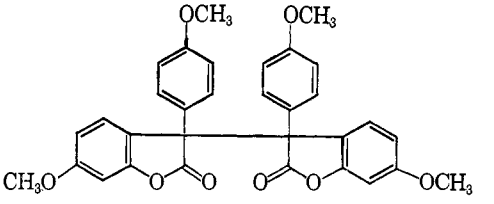
CLXII

been discussed. Finally, it should be mentioned that a third isomer, melting at 206° (281) is the $\Delta^{\beta,\gamma}$ isomer CLV. It is obtained by the treatment of α-phenyl-β-benzoylpropionitrile in acetic acid with hydrogen chloride. This compound shows a carbonyl absorption at 1795 cm.$^{-1}$, consistent with the $\Delta^{\beta,\gamma}$ structure (278).

A few other bislactones may be mentioned (209, 299, 358). These compounds show thermochromism due to their dissociation. These dimers oxidize benzyl alcohol to benzaldehyde and phenylhydrazine to azobenzene and are themselves reduced to monomers.



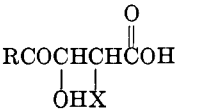
CLXIII



CLXIV

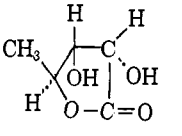
P. REACTION WITH OXIDIZING AGENTS

The behavior of isomeric butenolides toward alkaline potassium permanganate is sometimes used as a diagnostic test to determine the position of unsaturation. The $\Delta^{\alpha,\beta}$ isomers are usually hydroxylated to give dihydroxylactones, which may then be hydrolyzed to trihydroxy acids (212, 335). Thus, α,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide is converted to α,γ-diphenyl-α,β-dihydroxy-γ-butyrolactone (182). This is not a general test, since β,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide does not give the dihydroxy derivative (335). The $\Delta^{\beta,\gamma}$-butenolides, on the other hand, give hydroxyketonic acids, such as CLXV.

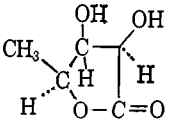


CLXV

With aqueous sodium chlorate in the presence of osmium tetroxide, β-angelica lactone gives a mixture of 5-deoxy-DL-ribonic acid γ-lactone (CLXVI) and 5-deoxy-DL-lyxonic acid (CLXVII) (213). With aqueous hypobromous acid, β-angelica lactone forms two di-

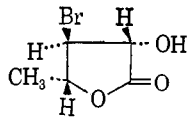


CLXVI

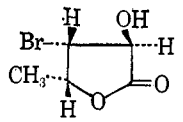


CLXVII

astereomeric forms of α-hydroxy-β-bromo-γ-valerolactone (CLXVIII and CLXIX) (215).

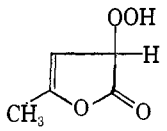


CLXVIII

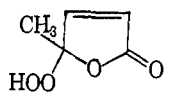


CLXIX

The autoxidation of α- and β-angelica lactones leads to the formation of hydroperoxides CLXX and CLXXI (280).



CLXX



CLXXI

Q. PYROLYSIS

The pyrolysis of α-angelica lactone or β-angelica lactone in the presence of silicon dioxide or pumice at 450–650° yields methyl vinyl ketone (41).

R. INTERCONVERSION OF $\Delta^{\beta,\gamma}$ AND $\Delta^{\alpha,\beta}$ ISOMERS

The $\Delta^{\beta,\gamma}$ isomers are usually regarded as labile isomers and $\Delta^{\alpha,\beta}$, the stable isomers. A number of methods are available for the conversion of the $\Delta^{\beta,\gamma}$ to the $\Delta^{\alpha,\beta}$ isomers, but not a single method has been mentioned in literature for the conversion of $\Delta^{\alpha,\beta}$ to $\Delta^{\beta,\gamma}$ isomers.

Of the several reagents employed for isomerization of $\Delta^{\beta,\gamma}$ isomers, tertiary amines seem to be the most commonly employed. Acetic anhydride and benzylamine have also been used (109).

S. TESTS FOR BUTENOLIDES

Many of the reactions enumerated above can be used to distinguish between the $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ isomers. Several authors have dealt with this problem (158, 189, 336).

The lactone carbonyl frequency in the infrared spectra of these compounds provides a clear distinction between these two types, the β,γ isomer absorbing at 1795 cm.$^{-1}$ and the α,β isomer at 1757 cm.$^{-1}$. In the ultraviolet region, a band near 217 mμ, due to the conjugated carbonyl chromophore, is characteristic of the $\Delta^{\alpha,\beta}$ compounds. For α- and β-angelica lactones, the refractive indices and densities may be used as criteria of purity (12–14) (Table VII). Dipole moments have also been used to identify the isomers (326). The difference in reaction of the two isomers with potassium permanganate has been discussed earlier, but this does not offer a simple laboratory test. The $\Delta^{\beta,\gamma}$ isomers condense with aldehydes in the presence of weak bases while the $\Delta^{\alpha,\beta}$ isomers fail to react.

TABLE VII

DENSITIES AND REFRACTIVE INDICES OF BUTENOLIDES

	d_4 (temp., °C.)	n
α-Angelica lactone	1.0904 (13.2)	1.44776
β-Angelica lactone	1.0822 (13.5)	1.45975
β,γ-Dimethyl-$\Delta^{\alpha,\beta}$-butenolide	1.0602 (16.2)	1.46393
α,α,γ-Trimethyl-$\Delta^{\beta,\gamma}$-butenolide	0.9818 (13.7)	1.43314
γ-Benzyl-$\Delta^{\beta,\gamma}$-butenolide	1.1537 (14.9)	1.56004
γ-Benzyl-$\Delta^{\alpha,\beta}$-butenolide	1.1173 (15.9)	1.52622

A detailed study of means of differentiation between $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ isomers was carried out with the angelica lactones (189). The following criteria were examined: (i) color reactions and reducing properties, (ii) ring opening by water and alkali, and (iii) ring opening involving the formation of anilides and esters.

In the Legal reaction with sodium nitroprusside at pH 11, β-angelica lactone gave a pink color, while the α isomer gave a strong red color which faded rapidly. The test with potassium ferricyanide proved less reliable. With ammoniacal silver nitrate, the $\Delta^{\beta,\gamma}$ isomer gave a black precipitate, while the $\Delta^{\alpha,\beta}$ isomer did not. Both gave positive tests with Tollens reagent. With 2,6-dichlorophenolindophenol at pH 11, the $\Delta^{\beta,\gamma}$ isomer gave a fading blue color which turned pink, while the $\Delta^{\alpha,\beta}$ isomer gave a permanent blue color (ii). On hydrolysis with water or alkali, the $\Delta^{\beta,\gamma}$ isomer gave the γ-keto acid, while the $\Delta^{\alpha,\beta}$ isomer remained unaffected (iii). With alcoholic hydrogen chloride, the $\Delta^{\beta,\gamma}$ isomer gave the ester while the $\Delta^{\alpha,\beta}$ isomer did not react. α-Angelica lactone reacts with aniline, while β-angelica lactone does not. The reaction with ammonia and amines has already been discussed. The behavior of butenolides under hydrogenation conditions furnished another method for distinguishing between the two isomers. The $\Delta^{\beta,\gamma}$ isomers give desoxy acids while the $\Delta^{\alpha,\beta}$ isomers form saturated lactones (60, 159).

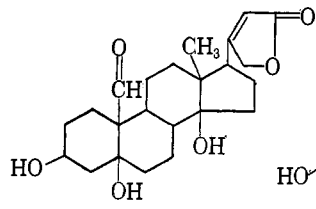
The Raymond reaction was used to differentiate between the normal and *allo* compounds. This involves the determination of the extinction coefficient at 620 mμ of a solution of the glycoside in alcohol containing *m*-dinitrobenzene and sodium hydroxide. The rates of decomposition of the colored compounds were determined, and the differences observed for the natural and anhydro glycosides may be caused by the different steroid skeletons attached in the β-position of the butenolide ring (49).

VIII. CARDENOLIDES

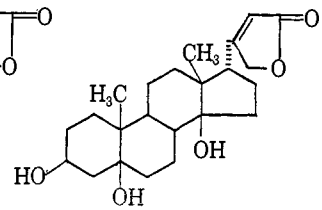
Cardiac glycosides consist of the cardenolide or aglycone moiety and a sugar residue, the latter aiding in solubilizing the aglycone unit. In this review, no attempt will be made to cover the chemistry of these compounds, as they have been described in great detail elsewhere (102, 282).

However, the structural formulas of strophanthidin

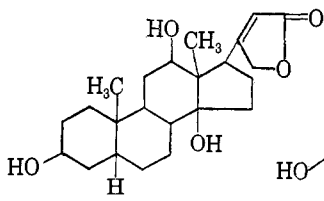
(CLXXII) and three other cardenolides will be given to stress the fact that these compounds are β-substituted $\Delta^{\alpha,\beta}$-butenolides.



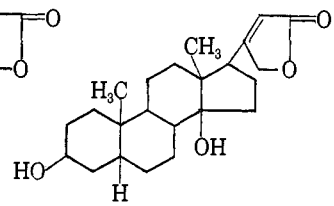
strophanthidin
CLXXII



periplogenin
CLXXIII



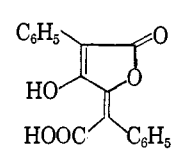
digoxigenin
CLXXIV



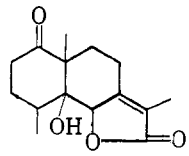
digitoxigenin
CLXXV

OTHER NATURALLY OCCURRING BUTENOLIDES

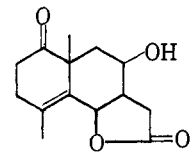
Vulpinic acid (CLXXVI) is α-phenyl-β-hydroxy-γ-phenylcarboxymethylene-$\Delta^{\alpha,\beta}$-butenolide (10). ψ-Santonin, which was originally assigned a $\Delta^{\beta,\gamma}$-butenolide structure (CLXXVII), has been shown to be CLXXVIIa (57, 62). The chemistry of these compounds will not be discussed here. An excellent review on these naturally occurring butenolides has been published recently (63b).



CLXXVI



CLXXVII



CLXXVIIa

IX. Structural–Biological Activity Relationships

The physiological activity of cardiac glycosides is due to the presence of the cardenolide or aglycone moiety. As already indicated, the cardenolides are C_{23} steroids having a $\Delta^{\alpha,\beta}$-butenolide as a side chain. The hydroxyl group in the C-14 position possesses a β-configuration. The stereochemistry of the ring system is similar to that of sterols or bile acids at C-8, C-9, C-10, C-13, and C-17. The *allo* compounds, which have no cardiac activity, have the α-configuration at C-14. It has been pointed out that the presence of a glycoside moiety is not essential for cardiac activity and that the sugar residue confers favorable solubility properties on the cardiac glycosides.

A number of β-substituted $\Delta^{\alpha,\beta}$-butenolides have been tested for cardiac activity (140). In addition, α-angelica lactone and β-angelica lactone were also tested. α-Arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides have all been tested for activity. One method of utilizing these butenolides as cardiac active compounds is to make them more soluble by adding aminopyrine, ethanolamine, and its salts. Much work has been done in this direction (20, 27, 52–56, 79, 98, 124, 148, 186, 244, 246–248, 255, 266, 267, 301, 315, 316, 351) but a discussion of this subject is not within the scope of this review. It may be mentioned, however, that none of the synthetic compounds tested possesses activity approaching that of the cardiac glycosides.

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X. References

(1) Adam, I. R., and Gianturco, M., *J. Am. Chem. Soc.*, **79**, 166 (1957).
(2) Albensi, G. H., and Tovaglieri, M., *Chim. Ind.* (Milan), **41**, 189 (1959); *Chem. Abstr.*, **53**, 19,872*d* (1959).
(3) Alguero, M., Bosch, J., Castaner, J., Castella, J., Castells, J., Metres, R., Pascual, J., and Serratosa, F., *Tetrahedron*, **18**, 1381 (1962).
(4) Allen, C. F. H., Davis, T. J., Stewart, D. W., and Van Allan, J. A., *Can. J. Chem.*, **34**, 926 (1956).
(5) Allen, C. F. H., and Frame, G. F., *Can. J. Res.*, **6**, 605 (1932).
(6) Allen, C. F. H., Frame, G. F., Normington, J. B., and Wilson, C. V., *Can. J. Res.*, **8**, 137 (1943).
(7) Ames, D. E., Bowman, R. E., and Grey, T. F., *J. Chem. Soc.*, 375 (1954).
(8) Angell, C. L., Gallagher, B. S., Ito, T., Smith, R. J. D., and Jones, R. N., "The Infra Red Spectra of Lactones," NRC Bulletin No. 7, National Research Council, Ottawa, Canada, 1960.
(9) Anschutz, R., and Montfort, W. F., *Ann.*, **284**, 1 (1895).
(10) Arata, Y., *J. Pharm. Soc. Japan*, **68**, 241 (1948); *Chem. Abstr.*, **48**, 3955 (1954).
(11) Armengaud, C., *Compt. rend.*, **254**, 3696 (1962).
(12) von Auwers, K., *Ber.*, **56B**, 1672 (1923).
(13) von Auwers, K., and Harris, L., *Ber.*, **62B**, 1678 (1928).
(14) von Auwers, K., and Wissebach, H., *Ber.*, **56B**, 731 (1923).
(15) Baddar, F. G., and Sherif, S., *J. Chem. Soc.*, 2309 (1960).
(16) Baddar, F. G., and Sherif, S., *J. Chem. Soc.*, 707 (1961).
(17) Badische-Anilin & Soda Fabrik, German Patent No. 804,-567 (1951).
(18) Baltazzi, E., and Davis, E. A., *Chem. Ind.* (London), 1653 (1962).
(19) Bardhan, J. C., *J. Chem. Soc.*, 2616 (1928).
(20) Beck, J. T., and Boulding, J. E., *J. Pharmacol. Exptl. Therap.*, **105**, 203 (1952).
(21) Berger, D. R., and Summerbell, R. K., *J. Org. Chem.*, **24**, 1881 (1959).
(22) Beschke, E., *Ann.*, **384**, 143 (1912).
(23) Beschke, E., *Ann.*, **391**, 111 (1912).
(24) Beschke, E., Kohres, G., and Marschall, E., *Ann.*, **398**, 265 (1912).

(25) Blood, C. T., and Linstead, R. P., *J. Chem. Soc.*, 2255 (1952).
(26) Blout, E. R., and Elderfield, R. C., *J. Org. Chem.*, **8**, 29 (1943).
(27) Boltze, K. H., *Wiss. Z. Friedrich-Schiller-Univ. Jena, Math. Naturwiss. Reihe*, 545 (1954–1955); *Chem. Abstr.*, **50**, 15,912 (1956).
(28) Boltze, K. H., Chemnitius, K. H., and Hofmann, H., *Pharmazie*, **11**, 319 (1956).
(29) Boorman, E. J., and Linstead, R. P., *J. Chem. Soc.*, 577 (1933).
(30) Borsche, W., *Ber.*, **47**, 1108 (1914).
(31) Borsche, W., *Ber.*, **47**, 2708 (1914).
(32) Borsche, W., *Ber.*, **48**, 842 (1915).
(33) Borsche, W., Hofman, P., and Kuhn, H., *Ann.*, **554**, 23 (1943).
(34) Borsche, W., Kettner, S., Giles, J., Kuhn, H., and Manteuffel, R., *Ann.*, **526**, 1 (1936).
(35) Borsche, W., and Sauernheimer, H., *Ber.*, **47**, 1645 (1908).
(36) Bougault, J., *Bull. soc. chim. France*, **23**, 20 (1918).
(37) Brassard, P., and Karrer, P., *Helv. Chim. Acta*, **43**, 262 (1960).
(38) Braude, E. A., and Timmons, C. J., *J. Chem. Soc.*, 3313 (1953).
(39) Bredt, J., *Ann.*, **236**, 225 (1887).
(40) Bredt, J., *Ann.*, **256**, 314 (1890).
(41) Bremner, J. G. M., and Jones, D. G., Imperial Chemical Industries, British Patent No. 601,922 (1948).
(42) (a) Breslow, R., Winter, R., and Battiste, M., *J. Org. Chem.*, **24**, 415 (1959); (b) Breslow, R., in "Molecular Rearrangements," de Mayo, P., Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter IV, pp. 241, 257.
(43) Brown, P., Burdon, J., Smith, T. T., and Tatlow, J. C., *Tetrahedron*, **10**, 164 (1960).
(44) Browne, C. I., and Lutz, R. E., *J. Org. Chem.*, **18**, 1638 (1953).
(45) Brugel, W., Dury, K., Stengel, G., and Suter, H., *Angew. Chem.*, **68**, 440 (1956).
(46) Buchta, E., and Satzinger, G., *Ber.*, **92**, 471 (1959).
(47) Buchta, E., and Moldenhauer, F., *Ber.*, **74B**, 1560 (1941).
(48) Campbell, N. R., and Hunt, J. H., *J. Chem. Soc.*, 1176 (1947).
(49) Canbäck, T., *Svensk Farm. Tidskr.*, **54**, 201, 225 (1950); *Chem. Abstr.*, **45**, 2961*g* (1951).
(50) Cavallito, C. J., and Haskell, T. H., *J. Am. Chem. Soc.*, **67**, 1993 (1945).
(51) Castaner, J., and Pascual, J., *J. Chem. Soc.*, 3962 (1958).
(52) Chemnitius, K. H., *Arch. Exptl. Pathol. Pharmakol.*, **236**, 392 (1959).
(53) Chemnitius, K. H., Doss, M., and Karl, M., *Acta Biol. Med. Ger.*, **4**, 216 (1960); *Chem. Abstr.*, **54**, 16,506*g* (1960).
(54) Chemnitius, K. H., and Hofmann, H., *Pharm. Zentrahalle*, **99**, 290 (1960); *Chem. Abstr.*, **56**, 899*h* (1961).
(55) Chem. Pharma. Fabrik, Hermann Thiemann, G.m.b.H. German Patent 1,058,697 (June 4, 1959); *Chem. Abstr.*, **55**, 9797*c* (1961).
(56) Chen, K. K., Steidt, F. A., Fried, J., and Elderfield, R. C., *J. Pharmacol. Exptl. Therap.*, **74**, 381 (1942).
(57) Cocker, W., Cross, B. E., and Hayes, D. H., *Chem. Ind.* (London), 314 (1952).
(58) Cocker, W., and Hornsby, S., *J. Chem. Soc.*, 1157 (1947).
(59) Cook, D., *Can. J. Chem.*, **39**, 31 (1961).
(60) Cornforth, J. W., and Cornforth, R. H., *J. Chem. Soc.*, 158 (1957).
(61) Dahn, H., and Rotzler, G., *Helv. Chim. Acta*, **431**, 1555 (1960).
(62) Dauben, W. G., and Hance, P. D., *J. Am. Chem. Soc.*, **7** 3352 (1953).
(63) Davey, W., and Tivey, D. J., *J. Chem. Soc.*, 1230 (1958).
(63a) Dean, F. M., "Naturally Occurring Oxygen Ring Compounds," Butterworths, London, 1963, pp. 1–81, 621.
(64) Dieckmann, W., *Ber.*, **47**, 1435 (1914).
(65) Ducher, S., *Bull. soc. chim. France*, 1259 (1959).
(66) Ducher, S., *Bull. soc. chim. France*, 430 (1960).
(67) Dunlop, A. P., and Peters, F. N., "The Furans," Reinhold Publishing Co., New York, N. Y., 1953.
(68) Dupont, G., Dulou, R., and Lefebvre, G., *Bull. soc. chim. France*, 339 (1951).
(69) Eisner, U., Elvidge, J. A., and Linstead, R. P., *J. Chem. Soc.*, 1051 (1951).
(70) El Assal, L., and Shehab, A. H., *J. Chem. Soc.*, 1020 (1959).
(71) El Assal, L., and Shehab, A. H., *J. Chem. Soc.*, 1658 (1961).
(72) Elderfield, R. C., *J. Org. Chem.*, **6**, 260 (1941).
(73) Elderfield, R. C., *Pharm. Acta Helv.*, **21**, 311 (1946).
(74) Elderfield, R. C., and Dodd, T. N., Jr., in "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1950, Chapter IV.
(75) Elderfield, R. C., and Blout, E. R., Eli Lilly Company, U. S. Patent 2,390,526 (1945).
(76) Elderfield, R. C., and Rubin, M., U. S. Patent 2,356,153 (1944).
(77) Elming, N., and Clauson-Kaas, N., *Acta Chem. Scand.*, **6**, 565 (1953).
(78) Els, H., Sobin, B. A., and Celmer, W. D., *J. Am. Chem. Soc.*, **80**, 778 (1958).
(79) Elsaid, F., *Proc. Pharm. Soc. Egypt, Sci. Ed.*, **35**, 81 (1953); *Chem. Abstr.*, **51**, 17,812 (1957).
(80) Elsaid, F., and Linnel, W. D., *Acta Pharm. Intern.*, **2**, 413 (1951); *Chem. Abstr.*, **48**, 9627 (1954).
(81) Elvidge, J. A., Linstead, R. B., and Sims, P., *J. Chem. Soc.*, 3386 (1951).
(82) Elvidge, J. A., Linstead, R. P., and Smith, J. F., *J. Chem. Soc.*, 1026 (1952).
(83) Erdmann, H., *Ann.*, **254**, 218 (1889).
(84) Erlenmeyer, E., *Ber.*, **36**, 2523 (1903).
(85) Erlenmeyer, E., *Ber.*, **37**, 3124 (1904).
(86) Erlenmeyer, E., *Ber.*, **38**, 3125 (1905).
(87) Erlenmeyer, E., and Braun, E., *Ann.*, **333**, 254 (1904).
(88) Erlenmeyer, E., and Kehren, C., *Ann.*, **333**, 238 (1904).
(89) Erlenmeyer, E., and Lattermann, A., *Ann.*, **333**, 268 (1904).
(90) Erlenmeyer, E., and Lux, M., *Ber.*, **31**, 2224 (1898).
(91) Eskola, S., *Suomen Kemistilehti*, **15B**, 17 (1942).
(92) Eskola, S., *Suomen Kemistilehti*, **30B**, 52 (1957); *Chem. Abstr.*, **53**, 16,014*d* (1959).
(93) Eskola, S., Hakkinen, H. M., and Niemi, E. L., *Suomen Kemistilehti*, **32B**, 105 (1959).
(94) Eskola, S., Sade, K., Leppamaki, E., and Rinne, T., *Suomen Kemistilehti*, **28B**, 87 (1955); *Chem. Abstr.*, **49**, 7404*d* (1955).
(95) Eskola, S., Udd, K., Leppanen, K., and Stjernvall, G., *Suomen Kemistilehti*, **20B**, 13 (1947).
(96) Ettel, V., Semonsky, M., and Sikan, V., *Chem. Listy*, **46**, 232 (1952).
(97) Ettel, V., Semonsky, M., and Zikan, V., *Chem. Listy*, **46**, 634 (1952).
(98) Evans, W. C., Smith, B. S. W., Linstead, R. P., and Elvidge, J. A., *Nature*, **168**, 772 (1951).
(99) Fecht, H., *Ber.*, **38**, 1272 (1903).
(100) Feist, F., *Ber.*, **31**, 534 (1898).
(101) Fichter, F., and Sonnenborn, F., *Ber.*, **35**, 942 (1902).
(102) Fieser, L. F., and Fieser, M., "Steroids," Reinhold Pub-

lishing Co., New York, N. Y., 1959, Chapter 20, pp. 727–809.
(103) Fiesselmann, H., and Ehmann, W., *Ber.*, **91**, 1713 (1958).
(104) Filler, R., and Hebron, L. M., *J. Am. Chem. Soc.*, **81**, 391 (1959).
(105) Filler, R., and Leipold, H. A., *J. Org. Chem.*, **27**, 4440 (1962).
(106) Filler, R., Mark, L. H., and Piasek, E. J., *J. Org. Chem.*, **24**, 1780 (1959).
(107) Filler, R., and Miller, F. N., unpublished results.
(108) Filler, R., Piasek, E. J., and Leipold, H. A., *Org. Syn.*, **43**, 3 (1963).
(109) Filler, R., Piasek, E. J., and Mark, L. H., *J. Org. Chem.*, **26**, 2659 (1961).
(110) Filler, R., and Piasek, E. J., *J. Org. Chem.*, **28**, 3400 (1963).
(111) Fittig, R., *Ann.*, **208**, 48 (1881).
(112) Fittig, R., *Ann.*, **256**, 50 (1890).
(113) Fittig, R., *Ann.*, **268**, 88 (1892).
(114) Fittig, R., and Devos, F., *Ann.*, **283**, 293 (1895).
(115) Fittig, R., and Ginsberg, M., *Ann.*, **299**, 1 (1897).
(116) Fleck, F., Rossi, A., and Schinz, H., *Helv. Chim. Acta*, **32**, 998 (1949).
(117) Fleck, F., and Schinz, H., *Helv. Chim. Acta*, **33**, 146 (1950).
(118) Fleming, I., and Harley-Mason, J., *J. Chem. Soc.*, 4778 (1963).
(119) Foldi, Z., *Acta Chim. Acad. Sci. Hung.*, **6**, (1955).
(120) Freeman, R., *Mol. Phys.*, **5**, 499 (1962).
(121) Fried, J., Linville, R. G., and Elderfield, R. C., *J. Org. Chem.*, **7**, 362 (1942).
(122) Friedman, L., and Long, F. A., *J. Am. Chem. Soc.*, **75**, 2832 (1953).
(123) Gaylord, N. G., "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956.
(124) Giarman, N. J., *J. Pharmacol. Exptl. Therap.*, **102**, 185 (1951).
(125) Gilman, H., Franz, R. A., Hewlett, A. P., and Wright, G. F., *J. Am. Chem. Soc.*, **72**, 3 (1950).
(126) Gilman, H., Vander Wal, R. J., Franz, R. A., and Brown, E. V., *J. Am. Chem. Soc.*, **57**, 1146 (1935).
(127) Gilmour, R., *J. Chem. Soc.*, **105**, 75 (1914).
(128) Grignard, V., Ed., "Traite de Chimie Organique," Vol. XI, Part I, Masson et Cie, Paris, 1945.
(129) Groth, R. H., *J. Org. Chem.*, **24**, 1709 (1959).
(130) Grove, J. F., and Willis, H. A., *J. Chem. Soc.*, 877 (1951).
(131) Hall, N., Haynes, J. E., and Lapworth, A., *J. Chem. Soc.*, **108**, 132 (1915); *Proc. Chem. Soc.*, **30**, 305 (1914).
(132) Hall, R. H., and Jacobs, D. I. H., *J. Chem. Soc.*, 2034 (1940).
(133) Hann, A. C. D., and Lapworth, A., *J. Chem. Soc.*, **85**, 1355 (1904).
(134) Hanna, C., and Schuler, F. W., *J. Am. Chem. Soc.*, **75**, 741 (1953).
(135) Haq, M. A., Kapur, M. L., and Ray, J. N., *J. Chem. Soc.*, 63 (1935).
(136) Hardegger, E., Plattner, P. A., and Blank, F., *Helv. Chim. Acta*, **27**, 793 (1944).
(137) Hardegger, E., Heusser, H., and Blank, F., *Helv. Chim. Acta*, **29**, 473 (1946).
(138) Hata, Y., Senoh, S., and Murakami, M., *Nippon Kagaku Zasshi*, **79**, 1447 (1958); *Chem. Abstr.*, **54**, 24,620c (1960).
(139) Haworth, R. D., and Sheldrick, G., *J. Chem. Soc.*, 636 (1936).
(140) Haynes, L. J., *Quart. Rev.* (London), **2**, 46 (1948).
(141) Haynes, L. J., and Jamieson, J. W., *J. Chem. Soc.*, 4132 (1958).
(142) Haynes, L. J., and Jones, E. R. H., *J. Chem. Soc.*, 954 (1946).
(143) Haynes, L. J., and Plimer, J. R., *Quart. Rev.* (London), **14**, 292 (1960).
(144) Heck, R. F., *J. Am. Chem. Soc.*, **85**, 657 (1963).
(145) Helberger, J. H., Ulubay, S., and Civelekoglu, H., *Ann.*, **561**, 215 (1949).
(146) Heusser, H., and Wuthier, H., *Helv. Chim. Acta*, **30**, 1400 (1947).
(147) Hochstein, F. A., *J. Am. Chem. Soc.*, **71**, 305 (1949).
(148) Hoffmann, H., and Chemnitius, K. H., *Wiss. Z. Friedrich-Schiller-Univ. Jena, Math. Naturwiss. Reihe*, 551 (1955).
(149) Houff, W. H., and Sell, H. M., *J. Am. Chem. Soc.*, **74**, 3183 (1952).
(150) Howell, W. N., and Robertson, A., *J. Chem. Soc.*, 587 (1936).
(151) Huan, *Bull. soc. chim. France*, [5] **5**, 1341 (1938).
(152) Huisgen, R., Konig, H., Binsch, G., and Sturm, H. J., *Angew. Chem.*, 370 (1961).
(153) Iwakura, Y., Nagakubo, K., and Hayashi, K., Japanese Patent 7506 (1956).
(154) Iwakura, Y., Nagakubo, K., and Hayashi, K., *Kogyo Kagaku Zasshi*, **59**, 476 (1956); *Chem. Abstr.*, **52**, 3759*f* (1958).
(155) Iwakura, Y., Tamikado, T., Fujimoto, Y., Ikegami, S., and Maruyama, M., *Kobunshi Kagaku*, **15**, 469 (1958); *Chem. Abstr.*, **54**, 11,555 (1960).
(156) Jacobs, W. A., and Elderfield, R. C., *J. Biol. Chem.*, **108**, 497 (1935).
(157) Jacobs, W. A., and Hoffmann, A., *J. Biol. Chem.*, **67**, 333 (1926).
(158) Jacobs, W. A., Hoffmann, A., and Gustus, E. L., *J. Biol. Chem.*, **70**, 1 (1926).
(159) Jacobs, W. A., and Scott, A. B., *J. Biol. Chem.*, **87**, 601 (1930).
(160) Jacobs, W. A., and Scott, A. B., *J. Biol. Chem.*, **93**, 131 (1931).
(161) Jacobs, W. A., and Scott, A. B., *J. Biol. Chem.*, **93**, 139 (1931).
(162) Japp, F. R., and Klingemann, F., *J. Chem. Soc.*, **57**, 662 (1890).
(163) Jeffery, D., and Fry, A., *J. Org. Chem.*, **22**, 735 (1957).
(164) Jones, E. R. H., and Whiting, M. C., *J. Chem. Soc.*, 1419 (1949).
(165) Jones, E. R. H., and Whiting, M. C., *J. Chem. Soc.*, 1423 (1949).
(166) Jones, E. R. H., Whitham, G. H., and Whiting, M. C., *J. Chem. Soc.*, 4623 (1957).
(167) Jones, R. N., Angell, C. L., Ito, T., and Smith, R. J. D., *Can. J. Chem.*, **37**, 2007 (1959).
(168) Jones, R. N., and Gallagher, B. S., *J. Am. Chem. Soc.*, **81**, 5242 (1959).
(169) Jones, R. N., Ito, T., and Angell, C. L., *Angew. Chem.*, 651 (1957).
(170) Judge, J. M., and Price, C. C., *J. Polymer Sci.*, **41**, 435 (1959).
(171) Justoni, R., *Gazz. chim. ital.*, **71**, 375 (1944).
(172) Kanevskaya, S. I., and Gnaeva, K. I., *Zh. Obshch. Khim.*, **21**, 1726 (1951).
(173) Karrer, P., and Testa, E., *Helv. Chim. Acta*, **32**, 1019 (1949).
(174) Katritzky, A. R., and Robinson, R., *J. Chem. Soc.*, 2481 (1955).
(175) Kemisk Vaerk, Koge. A/S, Danish Patent 74,271; *Chem. Abstr.*, **47**, 3351*h* (1953); British Patent 702,775 (1954).
(176) Klingemann, F., *Ann.*, **269**, 131 (1892).
(177) Klingsberg, E., *Chem. Rev.*, **54**, 59 (1954).

(178) Knowles, W. S., Kuck, J. A., and Elderfield, R. C., *J. Org. Chem.*, **7**, 372 (1942).
(179) Knowles, W. S., Fried, J., and Elderfield, R. C., *J. Org. Chem.*, **7**, 383 (1942).
(180) Kohler, E. P., and Conant, J. B., *J. Am. Chem. Soc.*, **39**, 1404 (1917).
(181) Kohler, E. P., and Conant, J. B., *J. Am. Chem. Soc.*, **39**, 1699 (1917).
(182) Kohler, E. P., and Kimball, R. H., *J. Am. Chem. Soc.*, **55**, 4632 (1933).
(183) Kohler, E. P., Hill, G. A., and Bigelow, L. A., *J. Am. Chem. Soc.*, **39**, 2405 (1917).
(184) Kohler, E. P., Peterson, W. D., and Bickel, C. L., *J. Am. Chem. Soc.*, **56**, 2000 (1934).
(185) Kohler, E. P., and Peterson, W. D., *J. Am. Chem. Soc.*, **56**, 2196 (1934).
(186) Krayer, O., Mendez, R., Moisset de Espanes, E., and Linstead, R. P., *J. Pharmacol. Exptl. Therap.*, **74**, 372 (1942).
(187) Kristensen-Reh, M., *Bull. soc. chim. France*, 882 (1956).
(188) Kucherov, V. F., Kuznetsova, A. I., Mavrov, M. V., and Alekseeva, E. F., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 484 (1962).
(189) Kuehl, F. A., Jr., Linstead, R. P., and Orkin, B. A., *J. Chem. Soc.*, 2213 (1950).
(190) Kugel, M., *Ann.*, **289**, 50 (1897).
(191) Kuhn, H., and Jerchel, D., *Ber.*, **76**, 413 (1943).
(192) Kumler, W. D., *J. Am. Chem. Soc.*, **60**, 2532 (1938).
(193) Kuschinsky, G., Lange, G., Scholtissek, C., and Turban, F., *Biochem. Z.*, **327**, 314 (1955).
(194) Lacey, R. N., *J. Chem. Soc.*, 821 (1955).
(195) Lacey, R. N., *J. Chem. Soc.*, 822 (1955).
(196) Lacey, R. N., British Patent 740,077 (1955).
(197) Lacey, R. N., British Patent 740,081 (1955).
(198) Lacey, R. N., *J. Chem. Soc.*, 3153 (1960).
(199) Lacey, R. N., and Graham, R. E., British Patent 740,076 (1955).
(200) Lapworth, A., *J. Chem. Soc.*, **85**, 1219 (1904).
(201) Lecocq, J., *Bull. soc. chim. France*, 183 (1951).
(202) Leipold, H. A., M.S. Thesis, Illinois Institute of Technology, Chicago, Ill., 1962.
(203) Leonard, R. J., U. S. Patent 2,809,203 (1957).
(204) Lespieau, R., *Compt. rend.*, **138**, 1051 (1904).
(205) Lespieau, R., *Compt. rend.*, **141**, 43 (1905).
(206) Lespieau, R., and Viguier, P. L., *Compt. rend.*, **146**, 294 (1908).
(207) Limpricht, H., *Ann.*, **165**, 283 (1873).
(208) Linville, R. G., and Elderfield, R. C., *J. Org. Chem.*, **6**, 270 (1941).
(209) Lowenbein, A., and Folberth, W., *Ber.*, **58**, 601 (1925).
(210) Lukes, R., *Collection Czech. Chem. Commun.*, **1**, 119 (1929).
(211) Lukes, R., *Collection Czech. Chem. Commun.*, **1**, 461 (1929).
(212) Lukes, R., and Jary, J., *Chem. Listy*, **49**, 1808 (1955); *Chem. Abstr.*, **50**, 9293 (1956).
(213) Lukes, R., and Jary, J., *Collection Czech. Chem. Commun.*, **24**, 3223 (1959).
(214) Lukes, R. L., Linhortova, Z., and Pliml, J., *Collection Czech. Chem. Commun.*, **25**, 502 (1960).
(215) Lukes, R., Nemec, J., and Jary, J., *Collection Czech. Chem. Commun.*, **24**, 3228 (1959).
(216) Lukes, R., and Prelog, V., *Collection Czech. Chem. Commun.*, **1**, 282, 617 (1929).
(217) Lukes, R., and Syohara, K., *Chem. Listy*, **48**, 560 (1954); *Collection Czech. Chem. Commun.*, **19**, 1205 (1954).
(218) Lukes, R., Koblicova, Z., and Blaha, K., *Collection Czech. Chem. Commun.*, **28**, 2182 (1963).
(219) Lutz, R. E., and Clark, C. T., *J. Org. Chem.*, **25**, 193 (1960).
(220) Lutz, R. E., Clark, C. T., and Feifer, J. B., *J. Org. Chem.*, **25**, 346 (1960).
(221) Lutz, R. E., and Couper, J., *J. Org. Chem.*, **6**, 77 (1941).
(222) Lutz, R. E., and Stewart, A. H., *J. Am. Chem. Soc.*, **58**, 1885 (1936).
(223) Lutz, R. E., and Stewart, A. H., *J. Am. Chem. Soc.*, **63**, 1143 (1941).
(224) Macek, K., Vancek, S., and Semonsky, M., *J. Chromatog.*, **9**, 60 (1962).
(225) Mark, L. H., M.S. Thesis, Illinois Institute of Technology, Chicago, Ill., 1959.
(226) Marrian, D. H., and Russell, P. B., *J. Chem. Soc.*, 753 (1946); Marrian, D. H., Russell, P. B., and Todd, A. R., *Biochem. J.*, **45**, 533 (1949).
(227) Marshall, E. R., Kuck, J. A., and Elderfield, R. C., *J. Org. Chem.*, **7**, 444 (1942).
(228) Marvel, C. S., and Levesque, C. L., *J. Am. Chem. Soc.*, **61**, 1682 (1939).
(229) Mayer, H., *Monatsh.*, **25**, 496 (1904).
(230) McRae, J. A., and Kuehner, A. L., *J. Am. Chem. Soc.*, **52**, 3377 (1930).
(231) Mendez, R., *J. Pharmacol. Exptl. Therap.*, **81**, 151 (1944).
(232) Meyer, W. L., and Vaughan, W. R., *J. Org. Chem.*, **22**, 1554 (1957).
(233) Micheel, F., Bode, G., and Siebert, R., *Ber.*, **70B**, 1862 (1937).
(234) Monnin, J., *Helv. Chim. Acta*, **40**, 1983 (1957).
(235) Moore, J. A., and Binkert, J., *J. Am. Chem. Soc.*, **81**, 6033 (1959).
(236) Mowry, D. T., *J. Am. Chem. Soc.*, **72**, 2535 (1950).
(237) Mowry, D. T., *J. Am. Chem. Soc.*, **75**, 1909 (1953).
(238) Mowry, D. T., Monsanto Chemical Co., U. S. Patent 2,591,589 (1952).
(239) Murakami, M., Semoh, S., and Hata, Y., *Mem. Inst. Sci. Ind. Res., Osaka Univ.*, **16**, 219 (1959); *Chem. Abstr.*, **54**, 22,555*i* (1960).
(240) Mustafa, A., Khattab, S., and Asker, W., *Can. J. Chem.*, **41**, 1813 (1963).
(241) Newman, M. S., Joshel, L. M., and Wise, P. H., *J. Am. Chem. Soc.*, **62**, 1861 (1940).
(242) Newman, M. S., and VanderWerf, C. O., *J. Am. Chem. Soc.*, **67**, 233 (1945).
(243) Nineham, A. W., and Raphael, R. A., *J. Chem. Soc.*, 118 (1949).
(244) Nordmann, S., and Klinger, W., *Acta Biol. Med. Ger.*, **6**, 416 (1961).
(245) Novak, L., and Protiva, M., *Chem. Listy*, **50**, 1610 (1956).
(246) Oettel, H., *Pharmazie*, **2**, 385 (1947).
(247) von Oettingen, W. F., *J. Pharmacol. Exptl. Therap.*, **36**, 335 (1929).
(248) von Oettingen, W. F., *J. Pharmacol. Exptl. Therap.*, **39**, 59 (1930).
(249) von Oettingen, W. F., *J. Am. Chem. Soc.*, **52**, 2024 (1930).
(250) Olsen, S., and Russwurm, H., *Ann.*, **639**, 1 (1961).
(251) Owen, L. N., and Sultanbawa, M. U. S., *J. Chem. Soc.*, 3105 (1949).
(252) Paist, W. D., Blout, E. R., Uhle, F. C., and Elderfield, R. C., *J. Org. Chem.*, **6**, 273 (1941).
(253) Pauly, H., Gilmour, R., and Will, G., *Ann.*, **403**, 119 (1914).
(254) Pelizoni, F., and Jommi, G., *Gazz. chim. ital.*, **89**, 1894 (1959).
(255) Philpot, J. St., and Stanier, J. E., *Biochem. J.*, 373 (1963).
(256) Piasek, E. J., Ph.D. Thesis, Illinois Institute of Technology, Chicago, Ill., 1962.
(257) Piasek, E. J., unpublished results.
(258) Pinazzi, C., Danjard, J. C., and Pautrat, R., *Bull. soc. chim. France*, 2433 (1961).

(259) Pinner, A., *Ber.*, **15**, 579 (1882).
(260) Piutti, A., *Gazz. chim. ital.*, **40**, 488 (1907).
(261) Plattner, P. A., Hardegger, E., and Bucher, H., *Helv. Chim. Acta.*, **28**, 167 (1945).
(262) Plattner, P. A., and Heusser, H., *Helv. Chim. Acta*, **28**, 1044 (1945).
(263) Plattner, P. A., and Heusser, H., *Helv. Chim. Acta*, **29**, 727 (1946).
(264) Plattner, P. A., Segre, A., and Ernst, O., *Helv. Chim. Acta*, **30**, 1432 (1947).
(265) Posternak, T., and Susz, J. P., *Helv. Chim. Acta*, **39**, 303 (1957).
(266) Pujman, V., *Ceskoslov. Akad. Ved.*, **66**, 1 (1956); *Chem. Abstr.*, **51**, 2171 (1957).
(267) Pujman, V., Dolezelova, V., and Prokopova, S., *Cesk. Onkol.*, **2**, 33 (1955).
(268) Pummerer, R., and Buchta, E., *Ber.*, **69**, 1005 (1936).
(269) Rambaud, R., and Ducher, S., *Compt. rend.*, **238**, 1231 (1954).
(270) Rambaud, R., Ducher, S., Broche, A., Brinl-Fritz, M., and Vessiere, M., *Bull. soc. chim. France*, 877 (1955).
(271) Rambaud, R., and Ducher, S., *Bull. soc. chim. France*, 466 (1956).
(272) Rambaud, R., Ducher, S., and Boudet, R., *Bull. soc. chim. France*, 1419 (1956).
(273) Ramirez, F., and Rubin, M. R., *J. Am. Chem. Soc.*, **77**, 2905 (1955).
(274) Ramirez, F., and Rubin, M. R., *J. Am. Chem. Soc.*, **77**, 3768 (1955).
(275) Rao, Y. S., and Filler, R., *J. Chem. Soc.*, 4996 (1963).
(276) Rao, Y. S., and Filler, R., *Chem. Ind.* (London), 280 (1964).
(277) Rao, Y. S., and Filler, R., unpublished results.
(278) Rao, Y. S., and Filler, R., to be published.
(279) Rasmussen, R. S., and Brattian, R. R., *J. Am. Chem. Soc.*, **71**, 1073 (1949).
(280) Rieche, A., Schulz, M., Seyfarth, H. E., and Gottschalk, G., *Fette, Seifen, Anstrichmittel*, **64**, 198 (1962); *Chem. Abstr.*, **57**, 4779 (1962).
(281) Robertson, M., and Stephen, H., *J. Chem. Soc.*, 863 (1931).
(282) Rodd, E. H., "Chemistry of Carbon Compounds," Vol. 1B, Elsevier Publishing Co., New York, N. Y., 1951.
(283) Rosenkrantz, H., and Gutt, M., *Helv. Chim. Acta*, **36**, 1000 (1953).
(284) Rothe, J., and Zimmer, H., *J. Org. Chem.*, **24**, 586 (1959).
(285) Rubin, M. R., *Dissertation Abstr.*, **17**, 2425 (1957).
(286) Rubin, M., Paist, W. D., and Elderfield, R. C., *J. Org. Chem.*, **6**, 260 (1941).
(287) Ruschig, H., Fritsch, W., and Lindner, E., German Patent 1,026,234; *Chem. Abstr.*, **54**, 10,961*i* (1960).
(288) Ruschig, H., Fritsch, W., and Lindner, E., German Patent 1,027,665 (April 10, 1958); *Chem. Abstr.*, **54**, 11,088*i* (1960).
(289) Russel, P. B., Todd, A. R., and Waring, W. S., *Biochem. J.*, **45**, 530 (1940).
(290) Ruzicka, L., U. S. Patent 2,386,749 (1947).
(291) Ruzicka, L., U. S. Patent 2,417,017 (1947).
(292) Ruzicka, L., and Plattner, P. A., U. S. Patent 2,428,171 (1947).
(293) Ruzicka, L., Plattner, P. A., and Heusser, H., *Helv. Chim. Acta*, **28**, 473 (1946).
(294) Ruzicka, L., Plattner, P. A., Heusser, H., and Ernst, O., *Helv. Chim. Acta*, **28**, 268 (1946).
(295) Ruzicka, L., Plattner, P. A., Heusser, H., and Schlegel, W., *Helv. Chim. Acta*, **27**, 186 (1944).
(296) Schmitt, G. J., and Schuerch, C., *J. Polymer Sci.*, **49**, 287 (1961).
(297) Schinz, H., and Hinder, M., *Helv. Chim. Acta*, **30**, 1349 (1947).
(298) Schinz, H., and Rossi, A., *Helv. Chim. Acta*, **31**, 1953 (1948).
(299) Schonberg, A., and Mustafa, A., *J. Am. Chem. Soc.*, **73**, 2401 (1951).
(300) Schueler, F. W., and Hanna, C., *J. Am. Chem. Soc.*, **73**, 3528 (1951).
(301) Schueler, F. W., and Hanna, C., *Arch. Intern. Pharmacodyn.*, **86**, 91 (1951); *Chem. Abstr.*, **5**, 7238*f* (1951).
(302) Schulte, K. E., German Patent 1,066,578 (Oct. 8, 1959); *Chem. Abstr.*, **55**, 103,246 (1961).
(303) Schulte, K. E., Mleinek, I., and Schar, K. H., *Arch. Pharm.*, **291**, 227 (1958).
(304) Schulte, K. E., and Nimke, G., *Arch. Pharm.*, **290**, 597 (1957).
(305) Schulte, K. E., and Riesch, J., *Arch. Pharm.*, **292**, 125 (1959).
(306) Schulte, K. E., and Reiss, K., *Angew. Chem.*, **67**, 516 (1955).
(307) Semonsky, M., Ettel, V., Jelinek, V., Zikan, V., and Pujman, V., *Casopis Lekaru Ceskych*, **93**, 197 (1954).
(308) Semonsky, M., Rockova, E., Zikan, V., Kakac, B., and Jelinek, V., *Collection Czech. Chem. Commun.*, **28**, 377 (1962).
(309) Semonsky, M., Rockova, E., Cerny, A., Kakac, B., and Macek, K., *Collection Czech. Chem. Commun.*, **27**, 1939 (1962).
(310) Semonsky, M., Cerny, A., Kakac, B., and Subrt, V., *Collection Czech. Chem. Commun.*, **28**, 3278 (1963).
(311) Serratosa, F., *Tetrahedron*, **16**, 185 (1961).
(312) Shaw, E., *J. Am. Chem. Soc.*, **68**, 2510 (1946).
(313) Shono, T., and Hachihama, Y., *J. Chem. Soc. Japan*, **58**, 692 (1955).
(314) Sintesa, S. A., Belgian Patent 613,932 (1962); *Chem. Abstr.*, **57**, 13,692*g* (1962).
(315) Sistrom, W. R., and Stanier, R. Y., *Nature*, **174**, 513 (1954).
(316) Smets, G., *Mededel. Vlaam., Chem. Ver.*, **7**, 95 (1945); *Chem. Abstr.*, **41**, 3317*h* (1947).
(317) Smith, R. J. D., and Jones, R. N., *Can. J. Chem.*, **37**, 2092 (1959).
(318) Smith, W. T., Jr., and Hanna, C., *J. Am. Chem. Soc.*, **73**, 2387 (1951).
(319) Sobotka, H. H., and Rubin, J. J., U. S. Patent 2,390,335 (1945).
(320) Sondheimer, F., Stjernstrom, N., and Rosenthal, D., *J. Org. Chem.*, **24**, 1280 (1959).
(321) Spiegelberg, H., and Kirchensteiner, H., Jubile Vol. Emil Barell, 149 (1946); *Chem. Abstr.*, **41**, 3788*g* (1947).
(322) Stecher, E. D., and Clements, A., *J. Am. Chem. Soc.*, **76**, 503 (1954).
(323) Stecher, E. D., and Gelblum, E., *J. Org. Chem.*, **26**, 2693 (1961).
(324) Sternberg, H. W., Shukys, J. B., Donne, C. D., Markby, R., Friedel, R. A., and Wender, I., *J. Am. Chem. Soc.*, **81**, 2339 (1959).
(325) Stewart, J. M., and Wooley, D. W., *J. Am. Chem. Soc.*, **81**, 4951 (1959).
(326) Sukigara, K., Hata, Y., Kurita, Y., and Kubo, M., *Tetrahedron*, **4**, 337 (1958).
(327) Sultanbawa, M. U. S., Veeravagu, P., and Padmanathan, T., *J. Chem. Soc.*, 1262 (1960).
(328) Swain, G., Todd, A. R., and Warring, W. S., *J. Chem. Soc.*, 548 (1944).
(329) Syohara, K., *Chem. Listy*, **53**, 311 (1959).
(330) Syohara, K., *Collection Czech. Chem. Commun.*, **26**, 2058 (1961).

(331) Tarbell, D. S., and Weaver, C., *J. Am. Chem. Soc.*, **62**, 2747 (1940).
(332) Thiele, J., *Ann.*, **303**, 217 (1898).
(333) Thiele, J., *Ann.*, **306**, 145 (1899).
(334) Thiele, J., *Ann.*, **306**, 194 (1899).
(335) Thiele, J., *Ann.*, **319**, 129 (1901).
(336) Thiele, J., *Ann.*, **319**, 144 (1901).
(337) Thiele, J., and Mayr, E., *Ann.*, **306**, 171 (1899).
(338) Thiele, J., and Mayr, E., *Ann.*, **306**, 176 (1899).
(339) Thiele, J., and Rossner, H., *Ann.*, **306**, 204 (1904).
(340) Thiele, J., and Salzberger, N., *Ann.*, **319**, 196 (1901).
(341) Thiele, J., and Straus, F., *Ann.*, **319**, 155 (1901).
(342) Thiele, J., and Straus, F., *Ann.*, **319**, 211 (1905).
(343) Thiele, J., Tischbein, R., and Lossow, E., *Ann.*, **319**, 180 (1901).
(344) Thiele, J., and Wedemann, W., *Ann.*, **347**, 132 (1906).
(345) Thorne, L. H., *J. Chem. Soc.*, **39**, 343 (1881).
(346) Thorne, L. H., *Ber.*, 2263 (1885).
(347) Torrey, J. V. P., Kuck, J. A., and Elderfield, R. C., *J. Org. Chem.*, **6**, 289 (1941).
(348) Tsou, K. C., Barrnett, R. J., and Seligman, A. M., *J. Am. Chem. Soc.*, **77**, 4613 (1955).
(349) Unilever, N. V., German Patent 1,072,629 (Jan. 7, 1960); *Chem. Abstr.*, **55**, 19,949*c* (1961).
(350) U. S. Patent 2,761,869 (1956).
(351) Van Pinxteren, J. A. C., and Smithius, A. L. O. M., *Pharm. Weekblad*, **89**, 741 (1954).
(352) Vaughn, W. R., and Tripp, R., *J. Am. Chem. Soc.*, **82**, 4370 (1960).
(353) Vinogradnova, E. J., and Shemyakin, M. M., *J. Gen. Chem. USSR*, **16**, 1279 (1946).
(354) Walton, E., *J. Chem. Soc.*, 438 (1940).
(355) Wasserman, H. H., quoted in ref. 369.
(356) Wasserman, H. H., and Koch, R. C., *Chem. Ind.* (London), 428 (1957).
(357) Wasserman, H. H., and Koch, R. C., *J. Org. Chem.*, **27**, 35 (1962).
(358) Wasserman, H. H., Liu, T., and Wasserman, E. R., *J. Am. Chem. Soc.*, **75**, 2066 (1953).
(359) Wasserman, H. H., and Precopio, F. M., *J. Am. Chem. Soc.*, **76**, 1242 (1954).
(360) Wasserman, H. H., Waters, R. M., and McKeon, J. E., *Chem. Ind.* (London), 1795 (1961).
(361) Wells, P. R., *Australian J. Chem.*, **16**, 165 (1963).
(362) Whiting, M. C., *J. Am. Chem. Soc.*, **71**, 2946 (1949).
(363) Wiberg, K. B., and Hutton, T. W., *J. Am. Chem. Soc.*, **76**, 5367 (1954).
(364) Wieland, T., and Rothhaupt, R. K., *Ber.*, **89**, 1176 (1956).
(365) Wiley, P. F., and Weaver, O., *J. Am. Chem. Soc.*, **78**, 808 (1956).
(366) Wolff, L., *Ann.*, 229 (1885).
(367) Wolff, H., and Moyer, W. W., U. S. Patent 2,493,373 (1950).
(368) Wolff, H., and Moyer, W. W., U. S. Patent 2,493,375 (1950).
(369) Yates, P., and Clark, T. J., *Tetrahedron Letters*, 453 (1961).
(370) Young, F. G., *J. Am. Chem. Soc.*, **71**, 1346 (1949).
(371) Zacharius, R. M., and Talley, E. A., *J. Chromatog.*, **7**, 51 (1962).
(372) Zimmer, H., Gracian, D., and Rothe, J., *J. Org. Chem.*, **25**, 838 (1960).
(373) Zinin, N., *Ber.*, **5**, 1104 (1872).
(374) Zugravescu, I., Petrovanu, M., Leonte, C., and Borcea, A., *Analele Stiint. Univ. A. I. Cuza Iasi, Sect. I*, **3**, 325 (1957); *Chem. Abstr.*, **53**, 15,039*a* (1959).
(375) Zugravescu, I., Petrovanu, M., and Ralea, R., *Rev. Chim. Acad. Rep. Populaire Roumaine*, **7**, 633 (1962).
(376) Zymalkosky, F., *Arch. Pharm.*, **284**, 292 (1951).