Improved Preparation and Characterization of Unsaturated γ-Lactones (1a)

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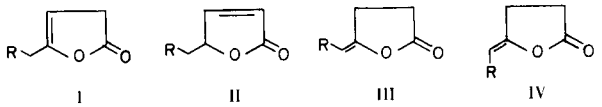
Improved, high yield procedures for the preparation of unsaturated γ-lactones (I-IV) from saturated γ-lactones (V) are described. Compounds V are first converted to the sodium salts of the corresponding γ-hydroxy acids (VI) (100%) which are oxidized within fifteen minutes to the γ-keto acids (VII) (75-85%) by bromine at *p*H 6-7.5. Acid-catalyzed reaction of VII with acetic anhydride at room temperature for fifteen minutes yields γ-acetoxy-γ-lactones (VIII) (70-90%). Pyrolysis of VIII at 200-330° yields I-IV (70-95%), the composition of which depends on whether strongly acidic contaminants have been completely removed from VIII prior to pyrolysis. In selected cases studied, fractional distillation permits the isolation of pure unsaturated lactones. Nmr has been extensively used to determine purity at each step and the composition of mixtures of I-IV.

Introduction.

Compounds that contain the unsaturated γ- and δ-lactone ring are reported to have carcinogenic (2-6) and antineoplastic activity (7,8), as well as other biological properties (9). Attempts have been made to correlate carcinogenicity with lactone structure but the validity of conclusions concerning the carcinogenicity of certain unsaturated lactones, based on work performed in the late 1950's and early 1960's, has been questioned (10,11). Our interest in the preparation, purification and characterization of unsaturated γ-lactones was sparked in part by our observation that certain unsaturated γ-lactones we were preparing for our own studies in carcinogenicity (12) were mixtures, a fact not known to the early investigators who had described the preparation of the same or similar compounds.

Since the validity of biological activity studies and their intercomparison between laboratories depend largely on the purity of the materials being tested, we initiated a study of improved, simplified rapid methods of synthesizing, separating and analyzing the exo- and endocyclic unsaturated lactones I-IV. In all cases, our objective was to obtain pure compounds but, failing that, we were also concerned with developing spectral and chromatographic (tlc, glc) methods for assessing the composition of mixtures of isomers.



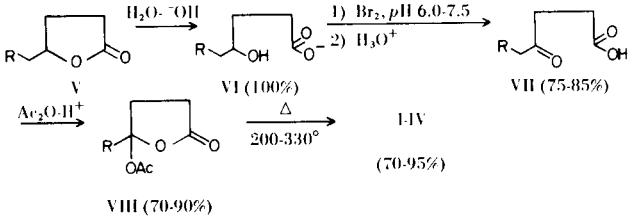
I II III IV

R = H, C_2H_5, *n*-C_3H_7, C_4H_9, C_5H_{11}, C_6H_{13}, C_7H_{15}, $C_{13}H_{27}$

Results and Discussion.

The following synthetic sequence was finally adopted for the preparation of homologous unsaturated γ-lactones I-IV (Scheme 1) (13):

(Scheme 1)



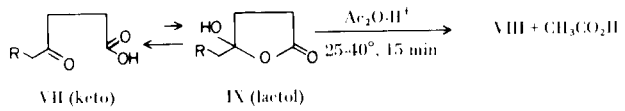
Saturated γ-lactones (V) are commercially available; in most cases purity exceeds 99% (glc, tlc) and no further purification is necessary. In contrast with literature procedures which recommend long reaction times and elevated temperatures, reaction of V with equimolar quantities of aqueous sodium hydroxide is complete in less than fifteen minutes at room temperature to give a homogeneous solu-

tion of the sodium salt VI. Isolation of the free hydroxy acid by acidification is both unnecessary and undesirable (some relactonization takes place).

The *p*H of the sodium salt solution is then adjusted to *p*H 6.0-7.5 (14) with aqueous sulfuric acid followed by oxidation at room temperature with an equimolar quantity of bromine while maintaining the *p*H with dilute aqueous sodium hydroxide to neutralize the hydrobromic acid formed (the *p*H of the reaction solution is continusously monitored with a *p*H meter). Neutral sodium hypobromite solution (see Experimental) can also be used as the oxidant but yields and purity of keto acids (VII) are somewhat lower. Most important, however, is that with either oxidant (sodium hypobromite or bromine) the reaction is complete within fifteen minutes; longer reaction times, as recommended in earlier literature reports (15,16) result in lower yields and purity of VII, as does the use of excess bromine (17). The keto acids are isolated by acidification to *p*H 1-2 followed by filtration or ether extraction. They are virtually pure without further workup but for our purposes we prefer to crystallize them from *n*-hexane. The conversion of V → VI → VII can be conducted in a single reaction flask and overall yields are good (75-85%).

The preparation of γ-acetoxy-γ-butyrolactones (VIII) from γ-keto acids was first described by Thiele (18) who refluxed keto acids for long periods with an equimolar quantity of acetic anhydride in the presence of acetyl chloride (a source of hydrochloric acid). Yields are only fair, dark colored products are obtained and unsaturated lactones form at the high reaction temperatures. Several other strong acid catalysts have been shown by us to be satisfactory (sulfuric and hydrochloric acid, boron fluoride, *p*-toluenesulfonic acid and Amberlyst-15 sulfonic acid ion exchange resin; trifluoroacetic acid is inactive). Most significant, however, is that (a) conversion of VII to VIII is complete within fifteen to thirty minutes at 25-40° (reflux is not recommended nor necessary) and (b) in our preferred procedure 70-90% yields of pure VIII are obtained with an equimolar quantity (or a slight excess to effect complete solution of solid VII) of acetic anhydride to VII and 2.5 weight % of Amberlyst-15 based on total reactants.

The intermediate in the conversion of VII to VIII is presumably the lactol (IX) which exists in equilibrium with its keto form (VII) (19). Although ir studies show



that the lactol tautomer is not present in significant concentrations in solutions of simple aliphatic γ-keto acids (20), acetic anhydride can displace the equilibrium to the right by acetylating IX.

Before acetoxylactones are pyrolyzed to unsaturated lactones the acid catalyst must be completely removed to reduce the number of unsaturated lactone isomers and polymeric products in the pyrolysate. Because Amberlyst-15 is insoluble it can be quickly and quantitatively separated by filtration. Complete separation of VIII from the other acid catalysts, however, is not so simple and is best accomplished by column chromatography which limits the preparative scale. Multiple recrystallization is time consuming, reduces the yields of VIII and complete elimination of catalyst does not occur (see below). Attempted chemical removal of acid catalysts by washing with base results in lower purity and yields of products (VIII).

During the preparation of acetoxylactones by the Thiele procedure (refluxing acetic anhydride overnight) unsaturated γ-lactones I and II are purported to form but not III and IV (21). The direction of acetic acid elimination depends on several interrelated factors, such as statistical, steric and thermodynamic effects (22). In pyrolyses of cyclic acetates, in which either exocyclic or endocyclic unsaturated isomers can form, the endocyclic isomers usually predominate due to their greater thermodynamic stability even though statistical and steric factors may favor the exocyclic isomers. Exocyclic isomers are easily converted to endocyclic isomers. Thus, methylenecycloheptane is isomerized to 1-methylcycloheptene in refluxing acetic acid, and methylenecyclopentane and methylenecyclohexane are converted to endocyclic isomers at room temperature by acetic acid containing a catalytic quantity of *p*-toluenesulfonic acid (23). We assume that lactones III and IV are probably also formed in the Thiele procedure but they are subsequently converted to the thermodynamically more stable endocyclic isomer (I) under the vigorous reaction conditions. The formation of unsaturated lactones II has no obvious explanation by theoretical arguments related solely to acetate pyrolysis and is assumed to occur by isomerization of I to the conjugated species II. Before preparative pyrolyses were conducted, a series of experiments was therefore designed to verify whether II forms by isomerization of I and, if so, whether the isomerization is thermally and/or chemically catalyzed.

α-Angelicalactone (I; R = H) free of acid catalyst, was selected as a model compound to check isomerization variables; samples used were free of the β-isomer (II, R = H) (24). (As little as 0.5% of the β-isomer in the α is detectable by nmr). Preparative glc treatment of the α-isomer resulted in 4-6% of isomerization to the β-isomer. The isomerization can be either a purely thermal process or a chemical one induced by interaction of the lactone with the Chromosorb solid support. To resolve this question, samples of pure α-angelicalactone were heated in carefully cleaned nmr tubes (25) for three minutes at 200° or over-

night at 100°; no isomerization is observed. However, when the α-angelicalactone contained 1% of sulfuric acid, *p*-toluenesulfonic acid or sodium acetate and the samples were heated to 200° for three minutes, isomerization to the β-isomer ranged from 40-60% (average, >50%). Acetic acid and γ-acetoxy-γ-valerolactone were catalytically inactive; phosphoric acid yielded an intractable tar. We conclude, therefore, that the isomerization of I → II is chemically catalyzed.

When γ-acetoxy-γ-valerolactone (VIII; R = H) is prepared from the keto acid using sulfuric acid as catalyst and the product is purified by chemical removal of the acid with sodium bicarbonate followed by multiple recrystallizations (but *not* by chromatography), heating it at 200° for three minutes in an nmr tube (25) results in an 85-90% conversion to a mixture of unsaturated lactones in the molar ratio I:II:III (R = H) of 3:1:1. Similar results are obtained in the pyrolysis of γ-acetoxy-γ-heptalactone (VIII; R = C_2H_5) at 200° for three minutes in an nmr tube. The molar ratio of lactones I:II:III:IV is 12:3:1:5. If chromatography is used in the purification of the acetoxylactone (VIII; R = H) an 80:20 mixture of I and III is obtained. If Amberlyst-15 is used as the catalyst in the preparation of the acetoxylactone (R = H) and then separated by filtration, I appears to be virtually the exclusive product.

Further evidence that isomerization requires chemical catalysis is obtained by the vacuum distillation of γ-acetoxy-γ-valerolactone prepared using Amberlyst-15 that had been separated by filtration. If the still temperature does not exceed 140° at 15-20 torr, the major fraction consists largely of α-angelicalactone (I; R = H) and a small quantity of acetic acid and acetic anhydride. The absence of exocyclic unsaturated lactone III (R = H) leads us to conclude that it must readily isomerize to I (R = H) in the presence of acetic acid. Evidence to support this conclusion is based on rapid pyrolysis studies; small quantities of III can then be detected (nmr).

γ-Acetoxy-γ-heptalactone (VIII; R = C_2H_5) was used as a model compound in establishing preparative pyrolysis conditions. Compound VIII prepared from the keto acid with sulfuric acid catalysis gives virtually the identical mixture of I-IV when pyrolyzed at 200° for three minutes in an nmr tube (25) or by passing a sample under a nitrogen blanket down a hot tube filled with glass beads at 330°. Unsaturated lactones, formed in 70-95% yield, consist of 50-55% I, 15-20% II, 5-10% III and 20-25% IV. When pyrolysis is conducted at a low rate and at low temperatures (below 175°), III and IV are not found as they undergo facile reconversion to VIII by readdition of acetic acid, as we have shown by model experiments. Both the nmr and hot tube pyrolyses qualify as fast, high temperature pyrolyses; thus, III and IV survive.

In addition to lactones I-IV, the pyrolysate contains some unpyrolyzed VIII (R = C_2H_5), acetic acid and polymer. Acetic acid must be removed prior to purification of unsaturated lactones by fractional distillation as it adds to the double bond and reforms VIII. Removal of acetic acid by washing the pyrolyzate with aqueous base is unsatisfactory owing to lactone hydrolysis and the introduction of basic impurities that catalyze isomerization and/or polymerization during distillation. Since acetic acid does not react with I at room temperature in the absence of added strong acid and it reacts only very slowly with II-IV, it is best removed by vacuum evaporation at room temperature. To remove other impurities that catalyze isomerization and polymerization during distillation, the acetic acid-free lactone mixture is dissolved in ether and passed through a short alumina column.

Pure unsaturated lactones I and IV are obtained by distillation of a mixture of I-IV through an Auto Annular Teflon Spinning Band Distillation apparatus (100-150 theoretical plates) but II and III are still obtained as mixtures (nmr, ir, uv and tlc analysis). Lactone II can be avoided as a product, however, by using Amberlyst-15 in the initial preparation of VIII or by using column chromatography to remove all traces of acidic isomerization catalysts from VIII; thus, pure III can also be obtained as long as II is absent at the start. The long distillation time required when the column is operated at peak efficiency causes some loss of unsaturated lactone products as polymeric residue but distillation appears to be superior to preparative glc.

The determination of purity of I-IV and assessment of the composition of mixtures is discussed in the Experimental Section.

EXPERIMENTAL

Materials and Instruments Used.

The following reagent grade chemicals were used as received: levulinic acid, α-angelicalactone and γ-decalactone (Aldrich); γ-heptalactone and γ-undecalactone (Fritzsche); γ-octalactone, γ-nonalactone and γ-undecalactone (Givaudan): Amberlyst-15 ion exchange resin (Mallinckrodt); trifluoroacetic and *p*-toluenesulfonic acids (Eastman); and acetic anhydride (J. T. Baker). All inorganic reagents were the purest grades; solvents were dried and purified by conventional methods (26). Ir: Perkin-Elmer 137 B or Unicam SP-1000. Nmr: Varian XL-100 or A60A. Uv: Perkin-Elmer 202. Tlc: Eastman Chromagram silica gel sheets without fluorescent indicators. Annular Teflon Spinning Band Distillation Column (Nester-Faust), F & M Model 500 Gas Chromatograph with thermal conductivity detection, and Thomas-Hoover melting point apparatus.

γ-Keto Acids (VII) from Saturated γ-Lactones (V). Typical "One-Pot" Procedures.

a) Bromine Oxidation.

γ-Undecalactone (V; R = C_6H_{13}) (181 g., 1.0 mole) was added to a magnetically stirred aqueous solution of sodium hydroxide (40 g., 1.0 mole) in water (250 ml.) at room temperature until a

homogeneous solution of sodium γ-hydroxyundecanoate (VI) was obtained (10-15 minutes). (Additional water was sometimes used to reduce viscosity and foam.) While the solution was continuously monitored with a *p*H meter, 50% sulfuric acid was added dropwise with cooling until the *p*H was 6.0-6.5 (14). The stirred solution was then cooled to 0° and maintained at that temperature while bromine (160 g., 1.0 mole) was added dropwise from an addition funnel over a 15-20 minute period (17). During the bromine addition the *p*H was held at 6.0-6.5 by adding aqueous sodium hydroxide (5-10 *M*) as needed to neutralize the hydrobromic acid formed. The *p*H was reduced to 1-2 by the addition of 50% sulfuric acid to the cooled, stirred reaction mixture. Any excess oxidant, as shown by starch-iodide paper, was destroyed by addition of aqueous sodium thiosulfate; this step was usually not required. The aqueous reaction mixture was extracted several times with ether and the combined ether solutions were washed several times with a concentrated aqueous sodium chloride solution. The ether solution was dried over anhydrous magnesium sulfate, filtered, and the ether was evaporated in a rotary evaporator. The solid residue was dissolved in the minimum quantity of boiling *n*-hexane and the solution was cooled slowly to room temperature (to avoid oiling out) and then to 0°. The precipitated γ-ketoundecanoic acid (VII) was filtered, washed with a small quantity of cold hexane and dried; m.p. 79-81° (75-85% yield); ir (potassium bromide): 3400-3600 (OH), 2860-2960 (CH) and 1690-1720 (C=O) cm^{-1}; nmr (carbon tetrachloride, TMS = 0): 0.92, 3H, t; 1.29, 8H, overlapping peaks; 1.59, 2H, p; 2.39, 2H, t; 2.59, 4H, s; 11.4, 1H, s. Other γ-keto acids similarly prepared and their melting points are: γ-ketoheptanoic, 51-52°, γ-ketooctanoic, 52-54°, γ-ketononanoic, 67-68°, γ-ketodecanoic, 68-70°.

Failure to control the *p*H, the use of excess bromine, and longer reaction times resulted in lower yields and colored reaction products.

b) Sodium Hypobromite Oxidation.

A solution of sodium hypobromite was freshly prepared by adding bromine (17.6 g., 0.11 mole) to a stirred solution of sodium hydroxide (4.0 g., 0.1 mole) in water (20 ml.) at 0° until the *p*H was 7.5. The solution was then utilized for the oxidation described in (a) above (0.1 mole scale) at the same *p*H and for the short reaction time (15 minutes). The yield of VII based on V was only 60%, however.

γ-Acetoxy-γ-lactones (VIII) from γ-Keto Acids (VII). Typical Procedures.

a) γ-Acetoxy-γ-valerolactone (VIII; R = H).

Acetic anhydride (102 g., 1.0 mole) was stirred magnetically with levulinic acid (116 g., 1.0 mole) at room temperature for 15 minutes in the presence of Amberlyst-15 ion exchange resin (5.0 g.). The reaction was mildly exothermic and reached a maximum temperature of 40° after 5-7 minutes; total reaction time was 15 minutes. The reaction mixture was filtered through a sintered glass funnel to remove the catalyst and acetic acid and acetic anhydride were separated from the filtrate by vacuum evaporation (*ca.* 5 torr) at a maximum temperature of 30°. Temperatures in excess of 30° led to slight decomposition of VIII. The solid residue was crystallized at 0° from ethyl ether; the yield of pure VIII R = H) was 110 g. (70%), m.p. 76-77°; ir (potassium bromide): 1750 and 1800 (C=O) cm^{-1}; nmr (deuteriochloroform, TMS = 0): 1.8, 3H, s; 2.1, 3H, s; 2.1-2.8, 4H, overlapping multiplets. No nmr absorptions were observed below 3.2 δ indicating the absence of unreacted keto acid and unsaturated lactones.

Owing to its thermal instability, the purity of VIII could not be determined by glc. Tlc of the crude reaction product on silica gel plates with a 50:50 chloroform:hexane solvent system cleanly separated VIII (major product) from the corresponding VII (minor) and I-IV (minor). Recrystallized VIII (R = H) gave a single tlc spot and all other criteria showed that it consisted of a single component.

b) γ-Acetoxy-γ-alkyllactones.

When R = alkyl rather than H, slight variations in procedure (a) above were required. Somewhat larger quantities of acetic anhydride were used to effect complete solution of VII. The crude acetoxylactone residues were liquids from which unreacted VII were separated by cooling a hexane solution to -10°. The crude VIII were estimated by nmr to be greater than 90% pure.

Compounds VIII were also prepared using concentrated sulfuric acid as catalyst (5 drops), instead of Amberlyst-15. After 15 minutes, the sulfuric acid was (ostensibly) neutralized with aqueous sodium bicarbonate solution before the acetic acid and excess acetic anhydride were removed by vacuum evaporation; yields were lower than with Amberlyst-15. Although the physical and spectral properties of VIII prepared with either catalyst system were identical, traces of isomerization catalyst clearly remained as the pyrolysis results later showed.

Model Studies on the Isomerization of Unsaturated Lactones.

a) GLC.

Pure α-angelicalactone (less than 0.5% β-isomer) was examined by glc using a procedure employed in the analysis of saturated γ-lactones (V). An F & M gas chromatograph with a 6′ x ¼″ column packed with 10% Apiezon L on Anachrom ABS was used: flow rate, 75 ml. He/min.; injector temperature, 300°; detector temperature, 300°, detector current, 100 milliamps. Approximately 4-6% of the β-isomer formed and was isolated by preparative glc.

b) Thermal.

α-Angelicalactone (50 mg.) was heated to 200° for three minutes or at 100° overnight in specially cleaned nmr tubes (25). The residue was dissolved in carbon tetrachloride; no nmr signals attributable to the β-siomer were observed.

Pyrolysis of VIII.

a) γ-Acetoxy-γ-valerolactone (VIII, R = H), prepared from VII (R = H) with sulfuric acid catalysis and multiply recrystallized from ether, was heated to 200° for three minutes in a specially cleaned nmr tube (25); conversion to unsaturated lactones averaged 85-90%. The distribution of unsaturated lactones I:II:III (R = H) was 3:1:1. The composition of the mixture was determined by integration from the nmr spectrum as each of the three isomers has an nmr spectrum unobscured by overlapping signals.

b) Compound VIII (R = H) was then purified by column chromatography on silica gel (44 g. to 1 g. of VIII) using chloroform:*n*-hexane for elution (1/1 v/v). Repetition of the pyrolysis (a) above gave a similar yield of a mixture of only two unsaturated lactones I and III (R = H) in a ratio of 4:1 (no β-angelicalactone could be detected).

c) When VIII (R = H), prepared with Amberlyst-15 catalyst, was vacuum distilled at 15-20 Torr at a still temperature not in excess of 140° (conditions analogous to the Thiele procedure) α-angelicalactone was the only unsaturated lactone present in the main fraction.

d) Thermogravimetric analysis in dry air (heating rate 40°/mm.) showed that decomposition of VIII is significant at 100° and rapid at 170°. Isothermal decomposition at 120° gave complete decomposition but 3 hours were required.

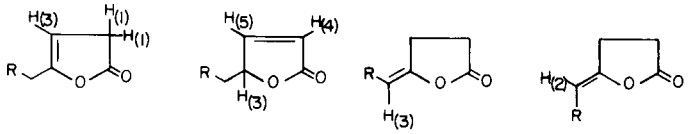
e) Compound VIII (R = C_2H_5), prepared from VII (R = C_2H_5) with sulfuric acid catalysis but *not* purified by chromatography, was dropped slowly (5 ml./hour) at 330° in a nitrogen atmosphere down a hot tube filled with glass beads (27). The pyrolysate was analyzed by nmr after vacuum evaporation of acetic acid coproduct at room temperature (yield 70-95%). Typically, the pyrolyzate contained 50-55% I, 15-20% II, 5-10% III and 20-25% IV and some unpyrolyzed VIII. An identical mixture of I-IV was obtained by heating VIII at 200° for three minutes in an nmr tube.

Purification of Unsaturated Lactones by Distillation.

Prior to distillation of the pyrolyzate from VIII (R = C_2H_5), it was dissolved in ether and passed through a short column of neutral alumina to remove colored and other impurities (acidic or basic) that caused isomerization during distillation. The ether was then evaporated at room temperature in a rotary evaporator and the residue was vacuum distilled using an Auto Annular Teflon Spinning Band Column (8-ml. charge). Fractions 1 and 2, b.p. 63-64° at 2.5 Torr, contained $\geq$ 98% I and Fraction 4, b.p. 72-73° at 2.5 Torr, contained $\geq$ 96% IV. The other fractions were mixtures of II and III. Pure III was obtained when II was absent from the pyrolyzate. This was effected by preparing VIII (R = C_2H_5) with the Amberlyst-15 catalyst or by purifying VIII, prepared with sulfuric acid catalysis, by silica gel chromatography, as already described.

Nmr Analysis of Lactones.

Protons 1,2,3,4 and 5 in unsaturated lactones I-IV have different chemical shift positions (TMS = 0), and they can be estimated by integration. Average shift positions (carbon tetrachloride) for the numbered protons in parentheses are: (1) 3; (2) 4.5: (3) 5.2; (4)



I II III IV

6; (5) 7.5 δ. Signal (3) in lactone III overlaps signal (3) in lactones I and II. The contributions of lactones I and II to the signal of (3) can be calculated from integrations of other characteristic protons in these molecules and deducted from the total integral of signal (3); the remaining area of (3) is then attributable to lactone III.

The α- and β-angelicalactones (I and II respectively; R = H) can also be assessed quantitatively by nmr (28,29). α-Angelicalactone (I) carbon tetrachloride, TMS = 0): CH_3, 1.9, doublet of triplets; $H_{(1)}$ 3.1, $H_{(3)}$ 5.1; J_{31} 2.5 Hz; $J_{3(CH_3)}$ 1.6; $J_{1(CH_3)}$ 2.7. β-Angelicalactone (II) (carbon tetrachloride, TMS = 0): CH_3, 1.4, d; H_3, 5.1 m; H_4, 6.0, dd; H_5, 7.5, dd.

In the preparation of γ-acetoxy-γ-lactones (VIII), the absence of nmr signals below 3.2 δ indicates the absence of unsaturated lactones or unconverted keto acids. The extent of pyrolytic decomposition of γ-acetoxy-γ-heptalactone (VIII, R = C_2H_5) was independently confirmed from the area of the methyl signals (*ca.* 1 δ) after the content of unsaturated lactones had been determined and their contribution to the total methyl signal could be calculated.

The nmr spectrum of γ-acetoxyvalerolactone (VIII, R = H) at 100 MHz gives relatively little useful information owing to overlapping signals (except for the two methyl singlets at 1.7 and 2.0 δ). A spectrum amenable to first-order analysis can be obtained by the use of 1.2 moles of the chemical shift reagent (Eu(fod)$_3$ to 1 mole of lactone in carbon tetrachloride. Spectra are given in the Ph.D. thesis of J. P. Wineburg.

Ir and Uv Spectroscopy.

α,β-Unsaturated γ-lactones can be easily distinguished from the β,γ-isomers by ir. The carbonyl absorption of α,β-isomers is at approximately 1750 cm^{-1} and the signal is split. That of the β,γ-isomer is at approximately 1800 cm^{-1} and is unsplit. The β,γ-isomers have a more intense C=C absorption at 1650-1685 cm^{-1} than do the α,β-isomers. Uv is a sensitive tool for showing the presence of conjugated isomers in nonconjugated isomers. The conjugated isomers show a strong absorption ($\epsilon \geq 10^5$) at approximately 220 nm, in the same region as the absorption of α,β-unsaturated esters.

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(14) Little difference in yields and purity of keto acids are observed within the *p*H range of 6.0-7.5. A *p*H range of 6.0-6.5 was most frequently employed as it appeared to give the most consistent results.

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(23) A. Cope, D. Ambros, E. Ciganek, C. F. Howell and Z. Jacura, *J. Am. Chem. Soc.*, 82, 1750 (1960).

(24) α-Angelicalactone contains a β,γ-double bond and β-angelicalactone contains an α,β-double bond. This nomenclature is confusing but is universally used.

(25) Nmr tubes cleaned in the usual fashion were successively rinsed 10x with distilled water, 10x with acetone, 10x with carbon tetrachloride and 10x with ether, then drained and inverted until dry. Failure to follow this laborious porcedure resulted in varying amounts of isomerization. The addition of acidic and basic species (0.005 g., sulfuric acid, *p*-toluenesulfonic acid or sodium acetate) resulted in extensive isomerization (> 50%) at 200° for three minutes.

(26) J. A. Riddick and W. B. Bunger, "Organic Solvents," Wiley-Interscience, New York, N. Y. 1970.

(27) The pyrolysis tube was 25 cm. long and fitted with 24/40 T joints at each end. The tube was carefully cleaned and prior to use it was rinsed with saturated aqueous sodium bicarbonate solution followed by thorough water rinsing and drying. Dimples near the bottom male joint held a wad of glass wool in place which supported the glass beads (≈ 5 mm. diameter). The tube was wrapped with insulated heating tape which also held a thermometer in place. The tube was capped with a pressure equalizing funnel equipped with a nitrogen inlet tube. The exit end of the tube was connected to an ice-cooled three-neck flask which had a water-cooled condenser in series with a dry ice/acetone cooled Dewar condenser in one of the openings. The entire apparatus was flushed with nitrogen for fifteen minutes before pyrolysis was started.

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