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On the α-CH-Acidity of Lactones and Esters; the Conformation of the *cis*-Ester Group

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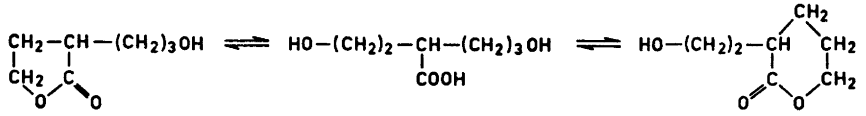
Lactones are shown to be more reactive than esters in reactions involving anion formation at the α-carbon atom. That lactones are thus more acidic than esters, could be verified by spectroscopic measurements of anion concentrations.

The different behaviour of γ- and δ-lactones in reactions involving the carbonyl carbon atom is related to the different conformational situation for the "*cis*-ester" group.

In the course of synthetic work towards 3-carboxy-hexane-1,6-diol (II) and similar compounds, designed for the purpose of studying the competition between γ- and δ-lactone formation (I and III), striking differences in chemical reactivity were observed between α-methylene groups of γ- and δ-lactones and open-chain esters.



I II III

Since the reactions were of alkylation, ester condensation, decarbalkoxylation, and decarboxylation type, it seemed that a greater stability of the anion from lactones could be a common explaining feature. The relative acidities were therefore determined by spectroscopic measurements of anion concentrations, and the expected difference was indeed observed.

In a final section, the problem of the intrinsically preferred conformation of the "*cis*-ester" group is discussed, especially in relation to reactivity differences at the carbonyl carbon, such as the well known stronger tendency of γ- than of δ-hydroxy acids for lactonization, as compared to polymerization.

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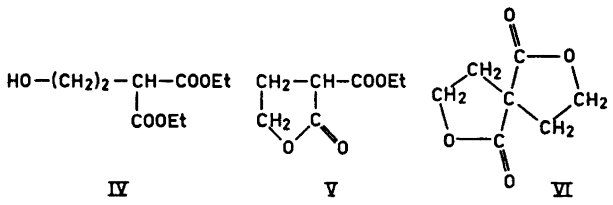
REACTIONS AT α-METHYLENE CARBON

It has been reported[1] that under Claisen condensation conditions γ-butyrolactone is acylated in the α-position by, *e.g.*, ethyl acetate. This suggests that the anion is formed preferentially from the lactone. An alternative explanation might have been that the lactone carbonyl group resists attack by the ethyl acetate anion, but this seems less likely since some self-condensation of the lactone occurs. Similar acylations take place[1] on substituted δ-lactones, while δ-valerolactone itself, as well as ε-caprolactone, are acylated only to 1 – 2 % and undergo rapid ring-opening to polymers instead.

One approach towards the carboxyhexanediol (II) was to hydroxyalkylate malonic ester first with 2-bromoethanol, and in a subsequent step with 3-bromopropanol. In the first step, however, the expected product (IV) was not formed. About half the malonic ester was recovered, and a small quantity of α-carbethoxy-γ-butyrolactone[2] (V) and a larger quantity of di(2-hydroxyethyl) malonic acid dilactone[3] (VI) were isolated. An accompanying compound, of less interest in this connection, has spectral properties indicating it to be the ethyleneketal of carbethoxyketene,[4] and must have been formed by transesterification.



Normally the CH-acidity of monoalkylated malonic ester is considerably lower than that of malonic ester itself,[5] so that dialkylation is unlikely before all molecules have become monoalkylated. It must therefore be assumed that the monoalkylated product (IV), as soon as it is formed, is immediately transformed to the lactone (V), and that the CH-acidity is thereby increased above that of the acidity of malonic ester. Further hydroxyalkylation and subsequent lactone formation to give spiro-dilactone (VI) would then become the favoured reaction.

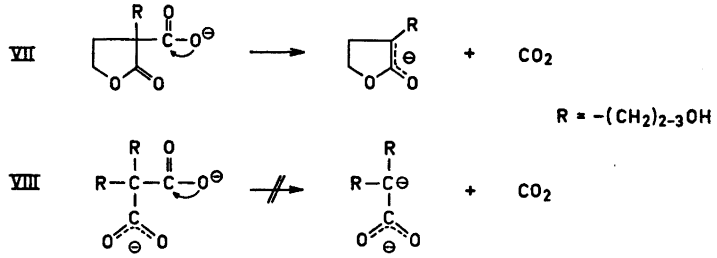
The above observation generated the idea that if a general method to prepare α-carbethoxylactones existed or could be developed, a subsequent hydroxyalkylation step would open a synthetic pathway to unsymmetrical spirolactones, and hence to the desired compounds (I – III). One such method is the reaction between diethyl malonate anion and alkene oxides,[2] but it is limited to the preparation of α-carbethoxy-γ-lactones. The possibility of preparing α-acyl-lactones from lactones by ester condensation in the presence of sodium or sodium hydride has already been mentioned.[1] * On the other

* α-Ethoxalyl-γ-butyrolactone can thus be synthesized[1] and was considered a possible precursor. However, attempts to split off carbon monoxide at 200° in the presence of glass powder[6] failed.

hand, it has been reported [7] that esters can be α-carbethoxylated by diethyl carbonate, although activation by, *e.g.*, an α-phenyl substituent is required to obtain good yields. It has also been reported [8] that substituted γ- and δ-lactones react with diethyl carbonate in the presence of alkali, but the yields of α-carbethoxylactones were not given. It was now found that γ-lactones and substituted δ-lactones * are converted to the α-carbethoxy derivative at or below the boiling point of diethyl carbonate in yields of 45 – 55 % for γ- and 35 – 40 % for δ-lactones, when sodium or sodium hydride was the base. δ-Valerolactone itself, as well as ε-caprolactone, gave no α-carbethoxylactone. Instead, the ring-opened "ester exchange" product, 5-carbethoxypentyl ethyl carbonate, was formed from ε-caprolactone.

The α-carbethoxy-γ-lactones thus obtained were hydroxyalkylated with 2-bromoethanol in low yield, or 3-bromopropanol in better yield, using potassium *t*-butoxide in *t*-butanol as a base. Ethylene oxide in the presence of piperidine [11] could also be used. α-Carbethoxy-δ,δ-dimethyl-δ-valerolactone gave no well defined product, since it isomerized extensively to γ-lactone under the reaction conditions.

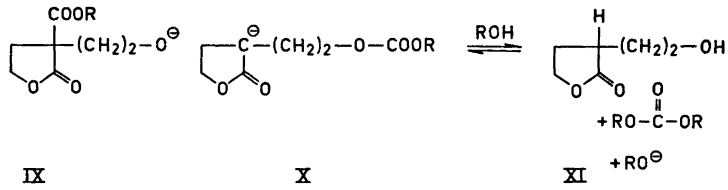
Hydrolysis and decarboxylation through VII could be effected in refluxing aqueous ethanol only when *one* equivalent of potassium hydroxide was used, and gave the dihydroxyacid lactone mixtures (for example I – III) as viscous distillable liquids in yields of 10 – 30 %. When decarboxylation was attempted with two or more equivalents of alkali, no reaction occurred even after refluxing for 48 h. Presumably, the lactone ring is then also opened, so that after hydrolysis a substituted malonic acid dianion (VIII) is formed which resists decarboxylation, as the resulting carbanion cannot be stabilized in a system carrying already a negative charge.



When the hydroxyalkylated α-carbethoxy-γ-lactones, instead of being hydrolyzed, were treated with potassium hydroxide in anhydrous ethanol below 30°, crystalline spiro-dilactones were formed in yields of up to 35 %. Although several spiro-dilactones have been described,[3,11,12] these are all of the symmetrical type (VI), whereas the present method allows also the preparation of unsymmetrical spiro-dilactones, even with respect to ring size (γ,δ). δ,δ-Dilactones, however, could not be obtained.

* An improved synthesis and product purity of δ,δ-dimethyl-δ-valerolactone [9] from δ-ketohexanoic ester was achieved by adapting the procedure [10] for the preparation of γ,γ-dimethyl-γ-butyrolactone through selective addition of methyl magnesium iodide to levulinic ester (see Exptl. part).

If this reaction is carried out at too high a temperature, the yield decreases strongly. The reason is that decarbethoxylation takes place, a common occurrence [13] with dialkylated malonic esters. Of particular interest in the present context is the stronger tendency for decarbethoxylation when one of the "ester" groups forms part of a lactone (IX). Thus, Pakendorff reports [14] that ethylene oxide hydroxyalkylation of malonic ester gives 2(2-hydroxyethyl)-γ-butyrolactone (XI), predominantly already at 60°, and exclusively at 120°. Again, a particular stability of the γ-lactone anion (X) seems to afford the explanation.



IX X XI

ACIDITY OF α-HYDROGENS

The above indications of differences in anion stability between lactones and esters prompted direct measurements of α-CH-acidities. The α-carbethoxy- and α-cyano-substituted compounds should be particularly suitable as they have pK_a-values in a range permitting easy measurements. Both γ- and δ-lactones were studied, since any observed difference might reflect a difference in the conformational situation of these rings.

Standard methods for acidity measurements are, however, problematic with lactones. Thus, conductivity measurements in water, which have been used for diethyl malonate,[15] are here excluded since some hydroxy acid is present in equilibrium with the lactone. Chemical shift changes in NMR-spectroscopy, actually observed when going from CCl_4 to pyridine solution, appears to be a measure of hydrogen bonding ability rather than of acidity, and steric and anisotropy effects [16] may also be disturbing.

Since anions of α-carbethoxy lactones and α-cyanolactones [17] have characteristic ultraviolet absorption, which is stronger than and discernible from that of any enol that may be present, it was possible to determine pK_a values in water for γ-lactones, as well as for cyanoacetic ester, by measuring this absorption in solutions of different pH, using the equation:

$$pK_a = pH - \log([A^-]/[HA])$$

The δ-lactones were too rapidly hydrolysed in alkaline solution to have their pK_a values determined in this way. Even for the γ-lactones and cyanoacetic ester, it was necessary to extrapolate back to zero time from measurements made at time intervals after the mixing of each solution to find its initial absorption.

In methanolic potassium hydroxide, the anions of the δ-lactones were sufficiently stable to allow direct measurements of their absorption. The ratio between the concentration of alkali, necessary for 50 % conversion to

anion, and the concentration of ester must be an expression of the acidity. When the logarithm of this ratio was plotted as a function of pK_a for those compounds whose acidity had been measured in water and for malonic ester, a linear relationship was not found throughout the whole series. However, within the group of α-carbethoxy-esters, and within the group of α-cyano-esters, linear relationship was assumed. From the two "standard curves" obtained in this way (Fig. 1), pK_a-values for the δ-lactones could thus be

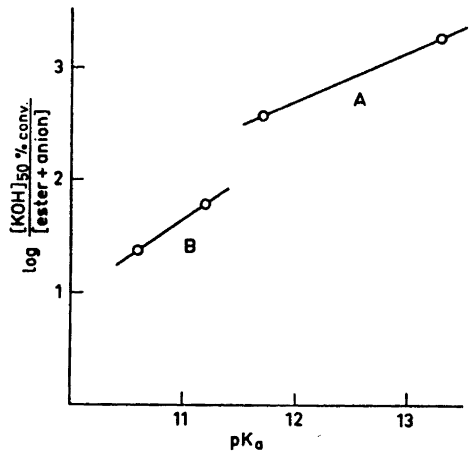


Fig. 1. The logarithm of the ratio between KOH concentration at 50 % conversion to anion and total concentration of lactone ester and its anion, in methanol solution, plotted against pK_a values determined in water solution: Curve A: α-Carbethoxylactones and diethyl malonate. Curve B: α-Cyanolactones and ethyl cyanoacetate.

Table 1. α-CH-Acidity of α-substituted esters and lactones.

	Abs. spectrum of anion λ_{max} (mμ)	ε	$\frac{[KOH]_{50\% \text{ conv.}}}{[ester+anion]}$	pK_a in H_2O	pK_a in MeOH
Diethyl malonate	260	3300	1900	13.3 [a]	
α-Carbethoxy-γ-butyrolactone	271	14300	360	11.7	
α-Carbethoxy-γ,γ-dimethyl-γ-butyrolactone	271	14500	360	11.7	
α-Carbethoxy-δ-methyl-δ-valerolactone	272	4600	360		11.7 [b]
α-Carbethoxy-δ,δ-dimethyl-δ-valerolactone	271	12700	430		11.9
Ethyl cyanoacetate	245	11400	62	11.2	
α-Cyano-γ-butyrolactone	253	10800	24	10.6	
α-Cyano-δ-valerolactone	253	8900	37		10.9 [b]

[a] Reference value [15] used.
[b] Less certain value because of partial ring opening during measurement.

estimated with an accuracy which of course depends on the validity of our assumption of linearity.

The pK_a values obtained are given in Table 1 together with data for reference compounds. As expected, lactones have considerably higher α-CH

acidity than corresponding esters. This is particularly marked for the α-carbethoxy-lactones, whose dissociation constants are about 25 – 40 times larger than that of malonic ester, while α-cyanolactones have only 2 – 3 times larger dissociation constants than cyanoacetic ester. Two of the δ-lactones seem to be slightly less acidic than the corresponding γ-lactones; for the α-cyano-δ-lactone, however, the lower acidity may be due to partial polymerization.

In the analogous series of α-acetylketones [18] the acidity increases on five-ring formation (α-acetylcyclopentanone), but decreases on six-ring formation (α-acetylcyclohexanone), as compared with the open chain (acetylacetone). However, the extensive enolization [18] of these compounds excludes a simple correlation with our lactones and esters.

THE PREFERRED CONFORMATION OF THE ESTER GROUP IN LACTONES

When the ester group has the freedom to choose conformation, it always takes up the planar *anti* conformation.[19] Its higher stability is perhaps understandable since the steric requirements of both the classical and the charged resonance structure are satisfied at the same time (Fig. 2). As to the "other"

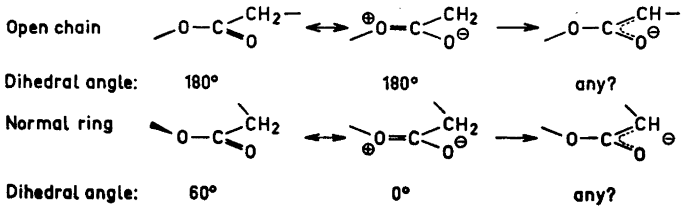


Fig. 2.

conformation, it is not easy to get information about its intrinsically preferred geometry, planar or nonplanar, since it can only be observed in ring structures where the ring itself imposes restrictions on it. It is also difficult to make a prediction, since a planar (*syn*)conformation would only satisfy the geometry of the charged resonance structure, while the classical structure would require a *gauche* conformation (Fig. 2) to avoid eclipsing; this conflict explains its reduced stability. What compromise conformation will be observed in each case must therefore be expected to depend delicately on ring size and the nature of ring substituents, especially if these form condensed ring structures.

The data of Table 1 indicate that the α-CH-dissociation energy is more than 2 kcal/mole smaller for lactones than for esters. If one accepts the estimated [19] energy difference of almost 4 kcal/mole between the neutral forms, this means that the lactone anion does remain less stable than the ester anion (Fig. 2), but that the difference has been reduced to 1 – 2 kcal/mole. This is most likely due to a freer torsion about single bonds next to the genuine mesomeric system of the anion (*cf.* aromatics, the nitro group, *etc.*[20]), so that the restrictions from the rest of the ring have been relaxed.

Earlier structural data for lactones [21] were mainly collected from compounds where the lactone ring forms part of a condensed system, and the observed conformation might therefore have been enforced by the rest of the molecule. Recently, however, X-ray structures have been reported for monocyclic γ- and δ-lactones of carbohydrate derivatives. In D-galactono-γ-lactone [22] carbon atoms 1, 2, and 4 lie, together with both oxygen atoms, roughly in one plane, while carbon atom 3 is 0.64 Å out of this plane, so that the ring resembles an "envelope". Nevertheless, the dihedral angle $C_2C_1OC_4$ is not exactly 0°, but 5°. In D-glucono-δ-lactone [23] this dihedral angle $C_2C_1OC_5$ is definitely larger, about 13°, the carbon atom 5 lying 0.28 Å out of the carbonyl plane, and the ring is intermediate between a cyclohexane chair and a cyclohexene half-chair.

The situation thus resembles that of the electronically related butadiene system, which in open-chain compounds adopts the very much preferred planar *anti*-conformation,[24] while for the "other" conformation a dependence on ring size is observed.[25] Exocyclic to a five-membered ring, a planar (*syn*) conformation, favouring a charged resonance structure with a ring double bond, is indicated by UV spectroscopy,[25] while exocylic to a six-membered ring a *gauche* conformation, favouring a classical uncharged structure with a ring single bond, is found.[24]

This difference between five- and six-membered rings is obviously connected with the well-known [26] tendency for cyclopentane derivatives to get away from their inherent conformational strain by conversion to relatively less strained cyclopentene derivatives, and the reluctance of the strainfree cyclohexane derivatives to be transformed to the inherently strained cyclohexene derivatives.

Returning to the lactones, γ- and δ-lactones do behave quite differently in many reactions other than those involving α-CH. Thus γ-lactones react more slowly by factors of 100 and 40 in acid and alkaline hydrolysis,[19] and resist polymerization to poly-esters,[27] while δ-lactones undergo such ring-opening even without catalysts.[27,28] This can now be understood on the simple conformational basis given above. Since the intermediate in base catalysis is formed by addition of OH^- or OR^- to the carbonyl group to form a tetrahedral carbon atom,[19] no double bond resonance structures are possible, and the rings become "saturated", which is favourable for a six-membered, but unfavourable for a five-membered ring. With δ-lactones, the base therefore adds relatively faster at the carbonyl group than it abstracts an α-proton, and so ring opening may occur before reaction at α-CH can take place. Similarly, the intermediate in acid catalysis is protonated on the carbonyl oxygen, and in order that subsequent attack by the nucleophile shall lead to ring opening, the positive charge must be on the carbonyl carbon atom and not on ring oxygen. This again means that the six-membered ring, which most easily renounces on ring double bond structures, reacts the fastest.

EXPERIMENTAL

The reaction between 2-bromoethanol and diethyl malonate. Sodium (2.3 g) was dissolved in dry ethanol (100 ml) and this solution of sodium ethoxide added dropwise to diethyl malonate (16 g) in ethanol (150 ml). The reaction mixture was then heated to 50°C for

15 min under stirring, whereafter 2-bromoethanol (12.5 g) was added, and heating (reflux) continued for 10 h under stirring. The still alkaline solution was neutralized with dry acetic acid, the precipitate removed by filtration, and the ethanol evaporated. Distillation gave unreacted diethyl malonate (8 g), b.p.$_{10}$ 80—125°, a further fraction, b.p.$_{0.1}$ 100—110° (0.5 g), identified as α-carbethoxy-γ-butyrolactone (V) by comparing its IR spectrum with that of an authentic sample,[2] and finally a fraction, b.p.$_{0.1}$ 100—117°, from which di-(2-hydroxyethyl)malonic acid dilactone (VI) crystallized, m.p. 110°, reported [3] 110°. The liquid part of this fraction had IR absorptions at about 1700 and 1625 cm^{-1} (reported [4] for the ethyleneketal of carbethoxyketene at 1692 and 1621 cm^{-1}) and a UV maximum at 241 mμ in ethanol (reported [3] at 236 mμ in tetrahydrofuran). The distillation residue was constituted for the main part (1 g) of the same dilactone, which was obtained pure on recrystallization from diethyl ether.

α-Carbethoxy-γ-butyrolactone (V). A, with sodium. Finely powdered sodium (7.7 g) in diethyl carbonate (80 g) was heated to 100° and γ-butyrolactone (29 g) in diethyl carbonate (25 g) was added dropwise. The rate of addition was maintained so that the reaction proceeded without further heating. After the addition was finished, the temperature was kept at 90° for 30 min, then cooled, and the reaction mixture poured into ice water (300 ml), to which had been added concentrated sulphuric acid (14 ml). The organic layer was separated from the water, and the water extracted with diethyl ether. The combined extracts were dried over sodium sulphate, and the ether, together with excess of diethyl carbonate, removed by evaporation at reduced pressure. Distillation gave α-carbethoxy-γ-butyrolactone (27 g=51 %), b.p.$_{11}$ 140—145° (reported [2] b.p.$_{25}$ 175°). IR and NMR spectra were identical with the spectra of an authentic sample.[2] The residue contained the condensation product [29] of two molecules of γ-butyrolactone.

B, with sodium hydride. γ-Butyrolactone (4.4 g) in diethyl carbonate (5 ml) was added dropwise to diethyl carbonate (10 ml) containing sodium hydride (1.2 g) kept in suspension by stirring and heating to 100°. In some cases heating to a somewhat higher temperature was necessary to start the reaction. After the addition was finished, the reaction mixture was heated to reflux for 2 h and then kept at about 100° overnight. The reaction product was worked up as under *A*, and gave the α-carbethoxy-γ-butyrolactone (3.6 g=46 %).

α-Carbethoxy-γ,γ-dimethyl-γ-butyrolactone. From γ,γ-dimethyl-γ-butyrolactone [10] (11.6 g) and sodium (2.3 g) the α-carbethoxy lactone was obtained in fair yield by method *A* (4.6 g=25 %). With sodium hydride (12 g) and lactone (45 g) by method *B* the yield was doubled (41 g=54 %). B.p.$_7$ 131—134° (reported [30] b.p.$_{0.5}$ 95°). (Found: C 58.26; H 7.60. Calc. for $C_9H_{14}O_4$: C 58.05; H 7.58). The IR and NMR spectra were consistent with the structure.

α-Carbethoxy-δ-methyl-δ-valerolactone. From δ-methyl-δ-valerolactone [31] (4 g) with sodium (1.4 g) the α-carbethoxy lactone was obtained by Method A (2.3 g=35 %). B.p.$_{10}$ 154—160°. (Found: C 58.14; H 7.50. Calc. for $C_8H_{14}O_4$: C 58.05; H 7.58).

α-Carbethoxy-δ,δ-dimethyl-δ-valerolactone. From δ,δ-dimethyl-δ-valerolactone (6.4 g), prepared as described below, and sodium (1.2 g) by Method *A* the α-carbethoxy lactone was obtained in fair yield (3 g=33 %). With sodium hydride (12 g) and lactone (50 g) by Method *B* the yield of α-carbethoxy lactone was similar (30 g=38 %). B.p.$_{10}$ 159—161°. (Found: C 60.02; H 8.07. Calc. for $C_{10}H_{16}O_4$: C 59.98; H 8.05). The IR and NMR spectra were consistent with the structure.

Attempted carbethoxylation of δ-valerolactone. When the same procedures were applied to δ-valerolactone, a product boiling over a very large range (about 100—200°/10 mm Hg) was obtained. Repeated fractionations did not give any product with a defined boiling-point interval.

Attempted carbethoxylation of ε-caprolactone. ε-Caprolactone (57 g) and sodium (11.5 g) in diethyl carbonate gave by Method *A* a product boiling between 125 and 160° at 10 mm Hg (25 g). Repeated distillation gave a fraction (10 g), b.p.$_{10}$ 145—155°, with NMR absorptions at δ 4.1 (multiplet), 2.2 (triplet), 1.5 (multiplet), and 1.2 (two triplets) in the ratios 3:1:3:3, which is as expected for 5-carbethoxypentyl ethyl carbonate.

δ,δ-Dimethyl-δ-valerolactone. To a solution of ethyl 5-oxohexanoate [32] (100 g) in a mixture of benzene (700 ml) and diethyl ether (100 ml) was added dropwise over 45 min at 0° a Grignard solution prepared from magnesium (19 g) and methyl iodide (115 g) in dry ether (350 ml). The reaction mixture was stirred vigorously for 20 h at room temperature, whereupon a solution of ammonium chloride (50 g) in water (400 ml) was

added slowly, and stirring continued for 5 h. Sulphuric acid (60 ml, 6 N) was finally added, the benzene layer separated, and the water layer extracted with ether. The combined organic solutions were dried over sodium sulphate and the solvents evaporated. Distillation gave δ,δ-dimethyl-δ-valerolactone (45 g), b.p.$_6$ 92—95° (reported[31] b.p.$_5$ 96°). The IR and NMR spectra were identical with those of an authentic sample.[9,31]

5-Hydroxy-2(2-hydroxyethyl)valeric acid lactones (I and III). Potassium (13 g) was dissolved in *t*-butanol (350 ml), and to this solution was added dropwise under stirring a solution of α-carbethoxy-γ-butyrolactone (53 g) in *t*-butanol (50 ml). 3-Bromopropanol (47 g) was then added, and the reaction mixture refluxed for 12 h. After cooling, precipitated potassium bromide was removed by filtration, and the solvent evaporated under reduced pressure. The residue was heated to reflux for 48 h in aqueous ethanol (35 ml water, 90 ml ethanol) containing potassium hydroxide (19 g). The ethanol was evaporated and the remaining aqueous solution acidified with sulphuric acid (pH 2—3) and extracted with ethyl acetate. The extract was dried over sodium sulphate and the ethyl acetate evaporated at reduced pressure. Distillation of the residue gave γ-butyrolactone (7—8 g), b.p.$_{15}$ 90—115°, and a mixture of γ- and δ-lactones of 5-hydroxy-2(2-hydroxyethyl)valeric acid (I and III) as a viscous, strongly hygroscopic oil, b.p.$_{15}$ 187—191°. (Found: C 57.55; H 8.38. Calc. for $C_7H_{12}O_3$ with 0.12 mole of water: C 57.55; H 8.38). The weight increases immediately in air after drying. IR absorption at 1760 cm^{-1} indicates that the γ-lactone is dominant in the mixture.

5-Hydroxy-2(2-hydroxy-2-methyl-propyl)valeric acid lactones. α-Carbethoxy-γ,γ-dimethyl-γ-butyrolactone (9.3 g) and 3-bromopropanol (7 g) gave under the same conditions the mixture of dihydroxy acid lactones (2.5 g=27 %) as a viscous, very hygroscopic oil, b.p.$_8$ 165—170°. (Found: C 61.12; H 9.40. Calc. for $C_9H_{16}O_3$ with 0.26 mole of water: C 61.12; H 9.36). The carbonyl stretching comes at 1760 cm^{-1}.

4-Hydroxy-2(2-hydroxy-2-methyl-propyl)butyric acid lactones. α-Carbethoxy-γ,γ-dimethyl-γ-butyrolactone (9.3 g) and 2-bromoethanol (6.3 g) gave, also by the same procedure, a mixture of the dihydroxy acid lactones, (0.8 g=9 %) as a strongly hygroscopic, viscous oil, b.p.$_8$ 160—165°. (Found: C 59.47; H 8.18. Calc. for $C_8H_{14}O_3$ with 0.20 mole of water: C 59.41; H 8.29). 3 g of decarboxylated starting material, γ,γ-dimethyl-γ-butyrolactone, distilled over below 140° at 8 mm Hg. The carbonyl stretching comes at 1760 cm^{-1}.

3-Hydroxypropyl-2-hydroxyethyl-malonic acid dilactone. α-Carbethoxy-γ-butyrolactone (V) (56 g) was added to a solution of potassium (13 g) in *t*-butanol (350 ml). Then 3-bromopropanol (50 g) was added and the reaction mixture heated to 60° with stirring for 12 h. Precipitated potassium bromide was filtered from the solution after cooling, the alcohol evaporated, and the residue dissolved in 20 % ethanolic potassium hydroxide (200 ml) and left at room temperature for 24 h. After evaporation of the alcohol at reduced presure below 30°, the residue was acidified with ice-cold dilute sulphuric acid and extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulphate and the solvent evaporated. Low-boiling products were removed by distillation and the dilactone crystallized from the residue. Recrystallization from diethyl ether yielded the dilactone as colourless crystals (17 g=30 %), m.p. 64—65°. (Found: C 56.46; H 5.98. Calc. for $C_8H_{10}O_4$: C 56.46; H 5.92).

2-Hydroxypropyl-2-hydroxyethyl-malonic acid dilactone. α-Carbethoxy-γ-methyl-γ-butyrolactone[30] (8.6 g), prepared here from diethyl malonate and propylene oxide, and 2-bromoethanol (6.3 g) gave by the same method a colourless liquid (1.5 g), b.p.$_9$ 180—190°, from which the dilactone crystallized. Recrystallization from diethyl ether gave colourless crystals (0.5 g=5 %), m.p. 65—70°, presumably an isomer mixture. (Found: C 56.49; H 6.02. Calc. for $C_8H_{10}O_4$: C 56.46; H 5.92). About 3 g of decarboxylated starting material, γ-methyl-γ-butyrolactone, distilled over below 160° at 9 mm Hg.

(2-Hydroxy-2-methyl-propyl)-2-hydroxyethyl-malonic acid dilactone. A mixture of α-carbethoxy-γ,γ-dimethyl-γ-butyrolactone (3.6 g), ethylene oxide (4 g), and piperidine (0.2 g) was set aside in a closed flask for 10 days at room temperature. Then 1 N sulphuric acid (20 ml) was added, the solution extracted with chloroform, the chloroform layer dried over sodium sulphate, and the solvent evaporated. Upon addition of a little benzene to the residue, the dilactone crystallized. Recrystallization from diethyl ether gave colourless crystals (1.2 g=33 %), m.p. 69—70°. (Found: C 58.50; H 6.72. Calc. for $C_9H_{12}O_4$: C 58.69, H 6.57).

Acidity measurements in water. The ultraviolet absorption of $5-10\times10^{-5}$ M solutions of ester or lactone, the concentration depending on the respective extinction coefficients, was measured at different pH values, using as a base sodium hydroxide. Several readings were made at intervals of 5 sec from the time of mixing the solutions, so that extrapolation back to zero time gave the initial absorption. The absorption values were plotted against pH, and from this curve was found the pH at 50 % conversion to anion, which directly gives the pK_a. The results are given in Table 1.

Acidity measurements in methanol. A similar concentration range ($5-20\times10^{-5}$) for ester or lactone was used, but extrapolation to zero time was not necessary, since the anions were relatively stable in alkaline methanol solution. Ultraviolet absorption was measured at different potassium hydroxide concentrations, the extinction plotted as a function of this concentration, and the potassium hydroxide concentration at 50 % conversion to anion found from this plot. The ratios between this concentration and total ester or lactone concentration are given in Table 1.

Ultraviolet spectra were obtained on a Perkin-Elmer 137 UV spectrophotometer and a Beckman DB spectrophotometer, infrared spectra on a Beckman-IR 5A spectrophotometer and NMR spectra on a Varian A-60A spectrometer.

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