## **458.** *Unsaturated Lactones and Related Substances.* (a) *Introduction.* (b) *Part I. Unsaturated γ-Lactones from Keto-acids. The Position of the Double Bond.*

By F. A. KUEHL, jun., R. P. LINSTEAD, and B. A. ORKIN.

An introduction is given to the series of papers.

Comparative experiments have been carried out on the various reactions used to distinguish between αβ- and βγ-unsaturated γ-lactones. For this purpose αβ- and βγ-angelicalactones and homoangelicalactones have been prepared, and also the lactones of 2-hydroxy*cyclo*hexylideneacetic acid and of 2-hydroxy*cyclo*hex-1-enylacetic acid. Analogous unsaturated lactones containing the *cyclo*pentane ring could not be obtained.

The diagnostic reactions examined were the reducing properties, various colour tests, and the reactions with water, alkali, ammonia, aniline, and alcoholic acid. Of these, clear-cut and reliable differences between the αβ- and βγ-isomerides were shown in the reactions with alcoholic acid and with aniline. The colour reactions and reducing tests are very sensitive to pH and of these the best were the reactions with dichlorophenolindophenol and with ammoniacal silver nitrate.

### (*a*) INTRODUCTION.

IN 1939 a programme of research was commenced on physiologically active unsaturated lactones. This included both a study of naturally occurring material such as the heart poisons of the digitalis group and synthetic studies. The work planned was interrupted by the war and subsequently by other duties. There has been considerable activity in this field during the past decade (see, *e.g.*, review by Haynes, *Quart. Reviews*, 1948, 46) and some of the work carried out by the senior author and his collaborators has been anticipated. The investigation of some aspects of the chemistry of these interesting materials is now being renewed, and it seems desirable as a first step to give some account of those aspects of our earlier work which are most complete and do not overlap with material published in the interval from other laboratories. This introduction is intended to act as an index to the four papers which follow, and which are necessarily somewhat disconnected.

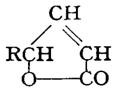
Part I deals with the preparation of unsaturated lactones from various keto-acids and with reactions which are said to be diagnostic of the position of the double bond (αβ- or βγ-). Part II describes the application of the Rosenmund reaction to the preparation of aldehydo-acids together with certain related topics. Parts III and IV deal with unsaturated lactones which contain a further functional group, either carboxyl or carboxylic ester. Part III describes the lactonisation of β-ketoadipic acid and the chemistry of the substances obtained. Part IV deals with the isomeric materials made by the lactonisation of muconic acid.

The work described in Parts I and II was carried out at Harvard in 1939—1941; that on muconic acid was commenced at Harvard at the same time and is now being continued at the Imperial College. Part III is a description of recent research (1949—1950) at the Imperial College, which is being pursued.

The pharmacological activity of a number of the unsaturated lactones described in these papers has already been reported (Krayer, Mendez, de Espanes, and Linstead, *J. Pharm. Exp. Ther.*, 1942, **74**, 372; Krayer, Mendez, and D. Todd, *ibid.*, 1943, **77**, 113).

## (*b*) PART I.

It was desired to make a direct comparison between pairs of unsaturated γ-lactones with the double bond in the αβ- and βγ-positions. For this purpose there were prepared the two angelicalactones (I and II; R = Me), and the two homoangelicalactones (I and II; R = Et), the preparation of which does not call for special comment. We have also prepared a pair of unsaturated lactones containing the *cyclo*hexane ring (III and IV). Since this work was done (Kuehl, Ph.D. Thesis, Harvard, 1942) the preparation of the αβ-*cyclo*hexane lactone (III) has been described by Cocker and Hornsby (*J.*, 1947, 1157) and by McCrae, Charlesworth, and Alexander (*Canadian J. Res.*, 1943, **21**, *B*, 1), and Newman and Van der Werf (*J. Amer. Chem. Soc.*, 1945, **67**, 233) have described preparations of both of the lactones. In our synthesis, *cyclo*hexanone-2-acetic acid (m. p. 73° in agreement with the above workers, but not with Chuang and Ma, *Ber.*, 1935, **68**, 871, who give m. p. 40°) was prepared from *cyclo*hexanone-2-carboxylic ester by conventional reactions. On direct pyrolysis the keto-acid gave a mixture of αβ- and βγ-unsaturated lactones in which the former predominated. Our results thus resemble those of Newman and Van der Werf (who used acetic anhydride for the lactonisation) and our products resemble those described in the literature. The solid lactone undoubtedly has the double bond in the αβ-position (see below).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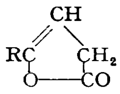
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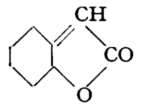
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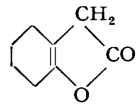
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We have also prepared the αβ-lactone by oxidising *cyclo*hexylideneacetic ester with selenium dioxide in acetic anhydride to ethyl 2-acetoxy*cyclo*hexylideneacetate. This on hydrolysis yielded 2-hydroxy*cyclo*hexylidene-1-acetic acid which on pyrolysis yielded the αβ-lactone (III) somewhat contaminated by isomeric impurity.

*Comparison between αβ- and βγ-Unsaturated Lactones.*—We have applied to these three pairs of lactones the reactions which have been suggested by various workers as being capable of distinguishing between the αβ- and βγ-isomerides, together with a few new diagnostic methods. The reactions examined can be divided into three groups: (i) Colour reactions and reducing properties. (ii) Ring fission by water and alkali. (iii) Ring fission involving the formation of esters and anilides.

The value of the various tests has to be interpreted with caution. It is a matter of difficulty to free the various lactones completely from all traces of their isomerides. Samples of αβ-lactones contaminated with traces of the much more reactive βγ-forms may give quite misleading results in colour and reducing reactions. This difficulty does not apply with the same force to reactions in which stoicheiometric quantities are involved.

(i) The best known colour reaction for unsaturated lactones is the Légal reaction with nitroprusside. The usefulness of this test as a means for distinguishing between αβ- and βγ-isomerides depends upon careful control of the alkalinity of the solution. The best pH for this purpose is about 11·0 and under the conditions described in the Experimental section a considerable difference between the αβ- and βγ-forms is observable. In our hands the use of potassium ferricyanide as suggested by Linville and Elderfield (*J. Org. Chem.*, 1941, **6**, 273) gave unreliable results. Better than either of the foregoing was 2 : 6-dichlorophenolindophenol which with the βγ-compounds at pH 11 gave a blue fading quickly to a light pink whereas the αβ-compounds gave a permanent blue colour. We also examined the well-known capacity of unsaturated lactones to deposit silver from suitable solutions. We found ammoniacal silver nitrate to give quite distinct differences between αβ- and βγ-compounds whereas Tollens's reagent is immediately reduced by both types.

In general, our observations on these reactions are consistent with the view that the rapid reactions are those of the βγ-compounds, whilst those of the αβ-isomerides may be due to preliminary shift of the double bond to the reactive position, which only occurs readily at higher pH values.

(ii) *Fission by water and alkali.* The αβ-compounds which we examined were neutral in aqueous solution : the development of acidity is a useful indication of the presence of βγ-impurity. Thus, βγ-angelicalactone gave a solution in water of pH 4—4·5. When aqueous solutions of the βγ-compounds were boiled the corresponding γ-keto-acids were slowly formed.

The reactions with alkali are complex and several courses are open according to the experimental conditions. The βγ-compounds are abnormal, being opened rapidly to the salts of hydroxy-acids which are the enolic forms of γ-keto-acids and rearrange into the keto-forms. The αβ-lactones are more normal. They are less acidic and their initial fission is slower. From the alkaline solution obtained it is possible to regenerate some αβ-compound. However, a side reaction intervenes in the migration of the double bond (in either the opened or the unopened lactone) to the βγ-position followed by formation of γ-keto-acid. The extent of this process depends upon the reaction conditions and on the particular system under investigation. A full investigation of these complex reactions calls for refinements in technique which are at present being examined.

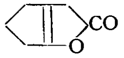
(iii) *Formation of esters and anilides.* None of the αβ-compounds examined reacted with alcoholic hydrogen chloride, whereas all three βγ-compounds were readily converted into the esters of the corresponding γ-keto-acids. These could be readily identified by the formation of ketonic derivatives. Under our experimental conditions normal keto-esters were obtained and not the pseudo-esters recently described by Langlois and Wolff (*J. Amer. Chem. Soc.*, 1948, **70**, 2624).

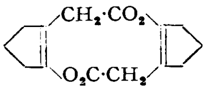
Lukeš and Prelog (*Coll. Czech. Chem. Comm.*, 1929, **1**, 182, 461, 617) showed that βγ-angelicalactone and homoangelicalactone were converted into the anilides of the corresponding γ-keto-acids by treatment with aniline. We have confirmed this reaction and find it to be useful for diagnosis. All three βγ-compounds give γ-keto-anilides, and none of the αβ-compounds reacts under the same conditions. The structure of the keto-anilides was confirmed by the preparation of ketonic derivatives. We also examined the reaction of ammonia but the results are less clear-cut and the products more difficult to isolate.

The many-sided physiological activity of unsaturated lactones has received much attention recently. The chemical reactivity of βγ-unsaturated γ-lactones is so high that the possibility must be borne in mind that the observed behaviour with biological systems may be due to artefacts and not to the lactones themselves. Results must therefore be interpreted with caution. The chemistry of lactones containing the system ·CH:C·O·CO· resembles that of acid anhydrides in many ways and there are analogies with other reactive systems, for example, vinyl ethers and 2 : 3-dihydrofurans.

We can summarise our experience as follows : The most reliable differences between αβ- and βγ-unsaturated lactones are shown by the reactions with alcoholic hydrogen chloride and with aniline. The dichlorophenolindophenol test is a useful colour reaction. The reactivities toward alkali are significantly different but the processes are complex.

(V.)





(VI.)

Experiments were also made with the object of seeing if an unsaturated lactone could be prepared of similar structure to (III) or (IV) but with a *cyclo*pentane ring in place of *cyclo*hexane.

*cyclo*Pentanone-2-acetic acid, however, behaved differently from the *cyclo*hexane analogue. Direct pyrolysis gave a high-melting substance corresponding to a dimer of the simple lactone (V). This may have the structure (VI). Reaction of *cyclo*pentanone-2-acetic acid with acetic anhydride gave an oil, $C_9H_{12}O_4$, apparently an enol acetate and not an acetoxy-lactone. Pyrolysis of this gave the same dimeric solid. These results are not unexpected; clearly the unsaturated lactone, (V) or a double-bond isomeride, would have a strained and unstable molecule.

## EXPERIMENTAL.

1. *Angelicalactones* (I and II; R = Me).—*Preparation*. Wolff's procedure (*Annalen*, 1885, **229**, 249) was used in preference to that of Bredt and of Thiele. The lævulic acid used must be free from its ethyl ester. The method of purification of the lactones used by Wolff is unnecessarily complex ; it is sufficient to distil the crude lactonic product twice through a good column. 52 G. of acid yielded 17—20 g. of $\beta\gamma$-lactone and 3—5 g. of $\alpha\beta$-lactone. More $\alpha\beta$-lactone could be prepared by isomerising the $\beta\gamma$-lactone by the method of Thiele, Tischbein, and Lossow (*ibid.*, 1901, **319**, 180). The physical properties of the two lactones were :

| | B. p./760 mm. | B. p./mm. | M. p. | $n_D^{20\cdot4}$. | $d_4^{20\cdot4}$. | $[R_L]_D$. |
|---|---|---|---|---|---|---|
| $\alpha\beta$- ........................ | 209° | 73°/3 | $<-80°$ | 1·4454 | 1·081 | 24·64 |
| $\beta\gamma$- ........................ | 167 | 53°/12 | +18 | 1·4476 | 1·091 | 24·04 |

*Colour reactions*. Standard solutions were prepared from 20 mg. of each lactone and 4 c.c. of 50% alcohol. One c.c. of this solution was added to an equal volume of freshly prepared aqueous sodium nitroprusside. ½ C.c. of this mixture was then added to 2 c.c. of each of the following solutions : 1% disodium hydrogen phosphate, 2% borax, ½% sodium carbonate, 1% sodium hydroxide, the pH's being 8, 9, 11, and 13, respectively. The following colours were observed :

| pH............ | 8. | 9. | 11. | 13. |
|---|---|---|---|---|
| $\alpha\beta$-Lactone ...... | Nil | Nil | Pink, fading fast | Immediate red, fading in 30 secs. |
| $\beta\gamma$-Lactone ...... | Nil | Light pink, becoming stronger | Immediate dark red, fading slowly | Bright red, fading in 30 secs. |

Similar tests were carried out with a 0·1% solution of 2 : 6-dichlorophenolindophenol in place of the nitroprusside, the resulting mixture being added to the buffer solutions.

| pH ...... | 8. | 9. | 11. | 13. |
|---|---|---|---|---|
| $\alpha\beta$-Lactone ... | No change | No change | Slow fading | Fades rapidly through green to colourless |
| $\beta\gamma$-Lactone ... | Fades to brownish-red | Fades rapidly to brownish-red | Fades very rapidly to brownish-red | Fades instantaneously to brownish-red |

Both lactones gave negative Schiff reactions and immediate deposition of silver from Tollens's reagent. Ammoniacal silver nitrate (prepared by adding ammonia dropwise to 10% silver nitrate until the precipitate just redissolved) was unaffected by the $\alpha\beta$-lactone and gave an instantaneous precipitate of grey-black silver with the $\beta\gamma$-lactone.

*Reactions with alcohol*. $\alpha\beta$-Angelicalactone (2·9 g.) was refluxed with 50 c.c. of 95% alcohol, 2 c.c. of 10% hydrochloric acid, and 6 c.c. of water (1 hour). The bulk of the alcohol was removed, and the residue taken up in ether and extracted with concentrated potassium carbonate solution and with water. The residue after removal of the solvent was distilled, the $\alpha\beta$-lactone being recovered, b. p. 45°/1 mm., neutral in aqueous solution, reducing Tollens's reagent but not ammoniacal silver nitrate, and giving no ketonic derivatives.

A similar experiment was carried out with 2·75 g. of $\beta\gamma$-angelicalactone. The neutral product (1·7 g.) distilled at 67°/3 mm. and gave the semicarbazone of ethyl lævulate, m. p. and mixed m. p. 148—149°.

*Reactions with aniline*. $\beta\gamma$-Angelicalactone (1·01 g.) was set aside with freshly distilled aniline (1·12 g.). After 24 hours the solid product was triturated with hexane, dried on a tile, and crystallised from hexane. The lævulic anilide obtained melted at 99—100° and gave a *semicarbazone*, m. p. 172° (Found : C, 58·0, 58·2; H, 6·6, 6·5; N, 24·2, 23·8. $C_{12}H_{16}O_2N_4$ requires C, 58·1; H, 6·5; N, 22·6%), and a 2 : 4-dinitrophenylhydrazone, m. p. 224°. The anilide is identical with that described by Lukeš and Prelog (*loc. cit.*) and by Helberger *et al.* (*Annalen*, 1949, **561**, 215). The ready formation of ketonic derivatives confirms the open-chain keto-formula assigned by Lukeš and Prelog.

A corresponding experiment with the $\alpha\beta$-lactone left a clear liquid after 4 days. From this, unchanged aniline and $\alpha\beta$-lactone were recovered.

2. *Homoangelicalactones* (I and II; R = Et).—Methyl homolævulate was prepared following Clutterbuck and Raper (*Biochem. J.*, 1925, **19**, 292) from $\beta$-carbethoxypropionyl chloride and ethylzinc iodide. On hydrolysis it gave homolævulic acid, m. p. 39—40° (Maire, *Bull. Soc. chim.*, 1908, **3**, 285, gives m. p. 36—37°). The yield was 66 g. of keto-acid from 100 g. of the half-chloride. The semicarbazone melted at 169—170° (Campbell and Thorpe, *J.*, 1910, **97**, 1315, give m. p. 176°). The keto-acid (66 g.) was kept for 3 hours with acetic anhydride (68 g.) and a few drops of acetyl chloride. The low-boiling product was distilled out at 60°/10 mm., and the residual acetoxy-lactone pyrolysed at about 200°/200 mm. The combined crude unsaturated lactone was washed in ethereal solution with aqueous

sodium hydrogen carbonate and distilled. The βγ-homoangelicalactone obtained boiled steadily at 49°/1·5 mm. and had $n_D^{27\cdot5}$ 1·4548; $d_D^{19\cdot8}$ 1·0662 (Found: C, 63·9; H, 7·3. Calc. for $C_6H_8O_2$: C, 64·25; H, 7·1%); yield, 57%. The αβ-isomeride was prepared by heating the βγ-lactone (26 g.) for 2 hours on the steam-bath with a few drops of triethylamine. The product was distilled, and the low fraction again treated with triethylamine. The united high fractions gave 15 g. of the αβ-homoangelicalactone, b. p. 72°/1·5 mm., $n_D^{27\cdot6}$ 1·4576, $d_4^{12\cdot3}$ 1·0704 (Found: C, 63·9; H, 7·3%).

The colour reactions were carried out as for the lower homologues:

Sodium nitroprusside:

| At pH...... | 8. | 9. | 11. | 13. |
|---|---|---|---|---|
| αβ-Lactone ... | No change | Faint pink | Pink | Strong red, changing to yellow |
| βγ-Lactone ... | Faint pink | Pink | Strong red, fading in 1 min. | Intense red, changing rapidly to yellow. |

2 : 6-Dichlorophenolindophenol:

| At pH...... | 8. | 9. | 11. | 13. |
|---|---|---|---|---|
| αβ-Lactone ... | ← No change in 5 minutes → | | | Fades to brown in 10 secs. |
| βγ-Lactone ... | Fades in 5 secs. | Fades in 3 secs. | Fades immediately to brown | |

| | Tollens's reagent: | Ammoniacal silver nitrate: |
|---|---|---|
| αβ-Lactone ... | Grey, turning to black in 5 secs. | No colour or precipitate in 5 mins. |
| βγ-Lactone ... | Immediate black precipitate | Black precipitate in 1 sec. |

βγ-Homoangelicalactone was refluxed with alcoholic hydrogen chloride as described for the lower homologue. The neutral product boiled at 62—63°/1 mm., had $n_D^{27\cdot6}$ 1·4235 and no reducing properties. It yielded the semicarbazone of ethyl homolævulate, m. p. and mixed m. p. 106—107°. When the αβ-lactone was treated similarly it was substantially unchanged, with b. p. 66·5—67°/1 mm. and the reducing properties described above.

When βγ-homoangelicalactone was left overnight with aniline (1 mol.) it formed a white solid which on crystallisation from benzene–hexane gave beautiful crystals of homolævulic anilide, m. p. 91—92°, in agreement with Lukeš and Prelog (*loc. cit.*). The *semicarbazone* formed plates, m. p. 161—162°, from 50% alcohol (Found: C, 59·9, 59·9; H, 7·0, 6·9; N, 21·9, 21·7. $C_{13}H_{18}O_2N_4$ requires C, 59·5; H, 6·9; N, 21·4%). Under the same conditions the αβ-lactone did not deposit any solid and was recovered unchanged.

3. *Lactones of* 2-*Hydroxy*cyclo*hexylideneacetic Acid and of* 2-*Hydroxy*cyclo*hex*-1-*enylacetic Acid* (III and IV).—"Molecular" sodium (22·9 g.) in dry benzene (850 c.c.) was treated with ethyl *cyclo*hexanone-2-carboxylate (170 g.). After 2½ hours' stirring on the steam-bath, ethyl chloroacetate (135 g.) was added in drops and the product heated overnight. Distillation of the neutral product yielded 127 g. (49%) of diethyl *cyclo*hexanone-2-carboxylate-2-acetate, b. p. 185—195°/25 mm. Hydrolysis of this (2 vols. of concentrated hydrochloric acid; 8 hours' refluxing) and fractionation of the product yielded 46·5 g. (60%) of *cyclo*hexanone-2-acetic acid, b. p. 147—152°/2 mm., together with a small forerun of unsaturated lactone (7·5 g.). After dissolution in alkali, followed by acidification, ether extraction, and distillation, the *cyclo*hexanone-2-acetic acid could be crystallised from benzene–hexane; it had m. p. 72·5—74° (Found: C, 61·4; H, 7·8%; equiv., 154·0, 156·1. Calc. for $C_8H_{12}O_3$: C, 61·5; H, 7·7%; equiv., 156·1). The semicarbazone of the acid melted at 134—135° and its ethyl ester at 195—196° (Chuang and Ma, *loc. cit.*, give 191—193°). Preparation of the acid from sodamide, *cyclo*hexanone, and ethyl chloroacetate was less satisfactory but gave the same product.

*Lactonisation.* The solid keto-acid (46·5 g.) was heated at 280° for one hour, and the residue distilled through a column. The yield of crude lactone (b. p. 105—115°/1 mm.) was 73%. Further fractionation yielded the αβ-lactone (III), b. p. 108—108·5°/1 mm. (42%), which could be further purified by crystallisation from ether at −50°. It then melted at 24° (Found: C, 69·4; H, 7·4. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·2%). The equivalent, determined by addition of excess of alkali and back titration, was 141·8 (Calc.: 138·1); $n_D^{24\cdot1}$ 1·5094; $d_D^{24\cdot1}$ 1·1245, whence $[R_L]_D$ 36·69, an exaltation of 0·76 unit.

A less satisfactory method of preparation is the following: ethyl *cyclo*hexylideneacetate (29 g.) was refluxed with 60 c.c. of acetic anhydride and 20 g. (1 mole) of selenium dioxide for 2½ hours. The product was cooled and filtered; the filtrate was warmed with water, neutralised with sodium hydrogen carbonate, and extracted with ether. The ethereal solution (Norite) was dried and freed from solvent, and the residue distilled. Ethyl 2-acetoxy*cyclo*hexylideneacetate distilled at 102—106°/2·5 mm. (25% yield). It was hydrolysed with 25% aqueous sodium hydroxide at room temperature. The 2-*hydroxy*cyclo*hexylideneacetic acid* produced had m. p. 154° (Found: C, 61·6; H, 7·7%; equiv., 158·5. $C_8H_{12}O_3$ requires C, 61·5; H, 7·8%; equiv., 156·1). It was heated at 240° for 15 minutes and the product separated into acid and pseudo-acid fractions. The acid fraction was again pyrolysed, and the united pseudo-acid fractions were distilled. The αβ-lactone (III), isolated in this way, resembled that already described in reducing properties, b. p. (127—133°/9 mm.), and refractive index ($n_D^{24\cdot2}$, 1·5105). The m. p. was low (5—10°), and the mixed m. p. intermediate (14—20°) (Found: C, 69·4; H, 7·2. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·2%).

To obtain the βγ-lactone (IV) the αβ-isomeride was repeatedly distilled at atmospheric pressure through a column. The low-boiling fraction was accumulated and distilled at 1 mm. The fraction of b. p. 88—93°/1 mm. gave the keto-anilide (see below) in 95% yield and hence must have been substantially pure; it could not be obtained crystalline (Found : C, 69·1 ; H, 7·6%).

*Reactions.* These were carried out as described for previous lactones.

Sodium nitroprusside :

| pH ...... | 8. | 9. | 11. | 13. |
|---|---|---|---|---|
| αβ-Lactone ... | ←—— No colour change ——→ | | | Yellow colour |
| βγ-Lactone ... | ←— Faint pink —→ | | Strong red, fading in 2 mins. | Strong red, fading to yellow in 30 secs. |

A positive Légal reaction was given by the αβ-lactone in higher concentrations.

2 : 6-Dichlorophenolindophenol :

| pH ...... | 8. | 9. | 11. | 13. |
|---|---|---|---|---|
| αβ-Lactone ... | ←—— No colour change ——→ | | | Colour faded in 30 secs. |
| βγ-Lactone ... | Colour faded to brown<br>in 1 min. | in 10 secs. | Colour faded immediately | Colour faded immediately |

The βγ-lactone gave an immediate black precipitate with Tollens's reagent and with ammoniacal silver nitrate. The αβ-lactone gave a positive Tollens's test in 2 seconds but no reaction with ammoniacal silver nitrate in 3 hours.

The αβ-lactone was substantially unchanged by boiling with water for 8 hours; the βγ-lactone gave 10% of keto-acid under these conditions. A solution of the αβ-lactone in 20% aqueous sodium hydroxide was kept overnight; the pseudo-acid fraction (38%) was unchanged lactone, the acid fraction (62%) was *cyclo*hexanone-2-acetic acid (m. p. and mixed m. p.).

The βγ-lactone was boiled for 1 hour with alcoholic hydrochloric acid as already described. No lactone could be detected in the product, which was identified as ethyl *cyclo*hexanone-2-acetate by the formation of the semicarbazone; m. p. and mixed m. p. 195—196°. The αβ-lactone was unchanged under these conditions.

The βγ-lactone was kept for 2 days at room temperature with aniline. The solid product was triturated with ether and crystallised from benzene–hexane. The *anilide* (95%) of *cyclo*hexanone-2-acetic acid had m. p. 119·2—120° (Found : C, 73·1 ; H, 7·3. $C_{14}H_{17}O_2N$ requires C, 72·7 ; H, 7·4%), and formed a *semicarbazone*, m. p. 196·5—197° (Found : C, 62·5 ; H, 6·9. $C_{15}H_{20}O_2N_4$ requires C, 62·5 ; 6·9%). A similar experiment with the αβ-isomeride gave unchanged starting materials.

4. *Attempted Preparation of Unsaturated Lactone from* cyclo*Pentanone-2-acetic Acid.*—*cyclo*Penantone-2-acetic acid (Linstead and Meade, *J.*, 1934, 940) was pyrolysed in 10-g. lots at 270° for 1 hour, during which time about 1 c.c. of water distilled out. Heating of the product at 20 mm. left the bulk behind as an intractable tar, and an indefinite distillate passed over of which a considerable portion boiled at 119°. Trituration of the distillate with ether left a crystalline solid. The ether-soluble portion yielded no lactonic product. The solid crystallised from benzene–hexane and melted at 169·5—171·5° and was probably the dimeric ester (VI) [Found : C, 67·6 ; H, 6·5% ; *M*(Rast), 252 ; equiv., 120·7. $C_{14}H_{16}O_4$ requires C, 67·7 ; H, 6·6% ; *M*, 248 ; equiv., 124]. No reactions typical of unsaturated lactones were given by this solid or by the liquid portion of the distillate.

*cyclo*Pentanone-2-acetic acid (5 g.) was heated for 30 minutes with acetic anhydride (4 g.) and two drops of acetyl chloride. The bulk of the acetic acid and anhydride was then removed by distillation, and the residue warmed with water and extracted by means of ether. Distillation yielded an oil, b. p. 111·5°/2·5 mm., apparently 2-*acetoxy*cyclo*pent*-1-*enylacetic acid* (Found : C, 58·5, 58·4 ; H, 6·6, 6·7. $C_9H_{12}O_4$ requires C, 58·7 ; H, 6·6%). The material was unsaturated, did not form a semicarbazone, and regenerated the parent keto-acid on alkaline hydrolysis. On pyrolysis, in an atmosphere of nitrogen, the enol acetate (25 g.) began to lose acetic acid at about 180°. Distillation of the product at 3 mm. yielded material of indefinite b. p. which was soluble in aqueous alkali, and gave a positive Légal but a negative Tollens reaction. The highest-boiling portion yielded some of the dimeride $C_{14}H_{16}O_4$, m. p. 170°, described above. The remainder of the material appeared to be essentially a mixture of *cyclo*pentanone-2-acetic acid and the unchanged enol acetate, and we obtained no reliable evidence of the presence of unsaturated lactone in it.

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